THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES

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THE INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES

Vol. 47 April–June, 2005 No. 2

CONTENTS

Guidelines for Management of Asthma: The Gaps Between Theory and Practice

[Indian J Chest Dis Allied Sci 2005; 47: 77-80]

Bronchial asthma is a complex disease with a very wide spectrum of severity in clinical presentations. Being a disease that is chronic and without a cure but still is quite controllable, it requires a continuing patient-physician participation and collaboration in treatment. The knowledge and skill required for successful control of asthma is likely to be available only with a physician with specialisation in pulmonary or internal medicine, being part of their post-graduate training curriculum. However, the number of asthmatics in any population is far greater than what can be managed by such trained persons. Therefore, a vast majority of asthmatics are managed by general or family physicians all over the world. The undergraduate teaching of bronchial asthma is confined to one or two lectures and an occasional case-discussion during the ward postings. The general physicians are, therefore, often handicapped in dealing with patients with bronchial asthma. As a result, asthma continues to be underdiagnosed and undertreated.

The last two decades have seen intensive efforts to standardise the treatment of bronchial asthma. This was necessitated by the epidemiological and observational evidence of increasing morbidity and mortality due to asthma despite the increased understanding of its pathogenesis as an inflammatory airways disease and availability of effective anti-asthma medications and newer delivery devices. These efforts have resulted in the development of clinical practice guidelines, statements and position papers for the general physicians, specialists and other health-care providers. There are more than forty guidelines available in different countries. The Global Initiative for Asthma[1], the National Asthma Education and Prevention Program[2] and the British Thoracic Society[3] guidelines have provided the basic pattern on which most of these have been developed. The guidelines in different countries have adapted these recommendations taking into account their own clinical evidence, local knowledge, attitudes and practices of physicians, and patient related-factors including socio-economic and cultural factors. The available guidelines are remarkably in agreement on most issues in management including diagnosis and assessment, monitoring, environmental manipulation, pharmacological and non-pharmacological interventions and patient education. There is a provision for referral to specialists.

The guiding principle and the belief behind the development and publication of guidelines was that if management principles were evidence-based and presented in an understandable and easy-to-follow practical format, doctors would automatically follow the recommendations and there would be a better care for patients with consequently better health outcomes and more cost-effective use of resources. This has remained a utopian objective. Despite widespread dissemination of clinical practice guidelines, adherence to them during patient care is often low, making this a major research, clinical, and public health concern. Although the interest in promulgation of clinical practice guidelines has greatly increased in the past decade, concern remains about the actual implementation of the guidelines at the organisational, clinical setting, and individual clinician levels[4].

What sounds good in theory may not be workable at the practical level. The relationship between theory and practice is never simple. Publishing a guideline document is not a guarantee that it will ever be read and still less that it will ever be acted on[5]. Many physicians

look at the guidelines as an intrusion into their rights to treat each patient as an individual and regard the imposition of guidelines as a threat. This is even more likely with senior members of the profession who would often like to be guided by their experience. It is usually not realised that the dividing line between "experience" and "bias" can be very thin and is often blurred. While it is easy to blame general physicians for not following the evidence-based recommendations for management, specialists too cannot be absolved. It has been shown that there was a low level of agreement in severity classifications of patients leading to substantial variability in the treatments recommended[6]. Granting that total agreement cannot be expected, yet efforts have to be made to ensure greater uniformity in approach.

However, this does not mean that changes have not occurred in the way the physicians now manage their asthmatic patients. There have been a series of audits and other activities aimed at promoting the use of guidelines. The British Thoracic Society, together with the National Asthma Campaign and the Royal College of Physicians, performed a study in 36 hospitals comparing the management of acute asthma in two months before the guidelines were published and in the same two months, one year later[7]. This study demonstrated that there were many deficiencies in the care process and that these were evident during admission, during the hospital stay, and on discharge. The greatest deficiencies occurred in patients cared for by non-respiratory specialists. For certain aspects of care, some hospitals only achieved the guideline recommendations in half or less of the patients under their care. One year later the study was repeated, and, disappointingly, there was no significant improvement in the standards of care[8]. When the study was repeated (but not in all the same hospitals), the national picture was much more encouraging, with use of inhaled corticosteroids and the provision of written self-management plans both rising. These data do demonstrate that the health services change by slow evolution and not by revolution —humans are generally resistant to change[5].

In the US, the experience has been similar. Although the asthma guidelines have been in existence for more than a decade, they have not been widely and consistently utilised by healthcare providers. The lack of adherence to published guidelines was observed to occur not only with patients living in poverty, but also with those who are managed in hospitals. This appeared in part to be related to a lack of understanding of the guidelines among physicians[9,10]. Legorreta *et al*[11] surveyed asthmatics receiving care in a health maintenance organisation and noted that 72% of respondents with severe disease reported having a steroid inhaler, of whom only 26% used it daily. In addition, although 26% of respondents reported having a peak flowmeter, only 16% used it on a daily basis. Similar observations noted in the "Asthma in America" survey also confirm that asthma management in the United States is falling short of the goals of the published guidelines.

The Asthma in America survey found the following: *(1)* although 70% of physicians said that they used spirometry on an ongoing basis, only 35% of asthmatics reported having had pulmonary function testing in the past year; *(2)* 83% of doctors reported prescribing a peak flowmeter, yet only 62% of patients had ever heard of the device (28% of asthmatics reported actually having a peak flowmeter, but only 9% actually used it at least once a week); and *(3)* 70% of physicians indicated that they prepared an action plan for their asthmatics, but only 27% of patients acknowledged having a written action plan. Eleven percent of physicians caring for asthmatics were unaware of the guidelines. Of those familiar with the guidelines, 32% reported that they always followed them, whereas 48% said they followed the guidelines most of the time. Finally, 92% of physicians surveyed agreed that anti-inflammatory drugs were essential in the management of persistent asthma. However, although 86% of physicians indicated that they would prescribe inhaled corticosteroids for moderate persistent asthma, only 19% of patients with persistent asthma reported taking inhaled steroids in the past month[12].

Yet, development of guidelines for management and their regular revision must go on. This is the best way to consolidate all available evidences on different aspects of management. Those responsible for the development of guidelines have to work along with those responsible for dissemination of knowledge to the practicing physicians. This would involve different arms of the health care administration, medical journals, pharmaceutical industry, and local medical associations. In addition to physicians, there are other providers (*e.g.*, nurses, psychologists, respiratory therapists, nutritionists, and health educators) who also have responsibility for different levels of interventions, as recommended in guidelines[4]. The challenge is multilevel and multidisciplinary. In the absence of a formal continuing medical education program for physicians, this is a formidable task.

Implementation of clinical practice guidelines by clinicians can be influenced in many ways. These include education, financial incentives, management strategies (such as collection and feedback of comparative data to clinicians, and cueing *via* computerised medical records), performance expectations or benchmarks, and alteration of structural aspects of the clinical environment (convenient availability of specialists, including nonphysician personnel)[13]. The implementation strategies have to be planned to suit local requirements and would obviously depend on the available resources. Grimshaw and colleagues[14,15] have described two types of educational strategies: *dissemination strategies*, designed to influence awareness, knowledge, and attitudes toward guidelines and their recommendations; and *implementation strategies*, designed to improve adherence to recommendations, turning changes in knowledge and attitudes to changes in practices.

There is considerable overlap in the types of activities and strategies that can be used to affect knowledge, awareness, attitudes, and skills. However, activities designed to affect knowledge and awareness are more informational, while those needed to affect attitudes and skills require interaction and opportunities to practice skills[4]. The traditional continuing medical education formats of lectures are good for increasing awareness, but have limited effectiveness in affecting practice. Electronic dissemination and print media also provide knowledge and increase awareness, but do little to affect attitudes, skills, and practice. Workshops offer opportunities for interaction and multiple teaching and learning strategies, but require more resources and clinician time than does information dissemination. Internet-based interactive curricula, interactive videos, and other electronic technologies are increasingly becoming available with the revolution in telecommunications and can be used for facilitating skill building.

There is little doubt that efforts to improve the implementation of evidence-based guidelines by clinicians will increase the quality of patient care. There is an urgent need to identify barriers to effective implementation. The educational programs should be designed with clear objectives and be tailored to local needs. The strategy, teaching techniques, and content must be appropriate for the objectives of the program and the audience. The focus should be on skill building and not merely information dissemination.

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ORIGINAL ARTICLE

What Do Parents of Asthmatic Children Know About Asthma?: An Indian Perspective

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ABSTRACT

Background. Despite the magnitude of the asthma problem, very little is known about the public perception about asthma.

Methods. This descriptive study was conducted to evaluate the knowledge, attitude and practice about the causation, treatment and prognosis of asthma amongst the parents of children with asthma. Subjects were parents of asthmatic children attending two exclusive paediatric hospitals at Chennai, India. A semi-structured pre-validated questionnaire, which included their general understanding on asthma, its triggers and management, was administered.

Results. One hundred parents of asthmatic children participated in this study. A diagnosis of asthma was accepted only by 39%, of which only three knew exactly what asthma means. Perception that asthma is contagious was observed by 26%, and 35% believed asthma to be a hereditary disease. Various dietary items were perceived as triggers. Most of the parents (62%) administered oral beta-agonist medication at home before proceeding to hospital, but majority were using them as cough medication. Only 13 were administering aerosol therapy at home. Nearly one-third of the parents opined that the disease might remit with advancing age.

Conclusions. General awareness of asthma in the community is poor. Patient education programme should augment awareness, eliminate social stigma and misconcepts in the community regarding asthma. Knowledge about the prevailing perception in the community would be the first step in achieving this.

Key words: *Asthma awareness, Patient education programme.*

[Indian J Chest Dis Allied Sci 2005; 47: 81-87]

INTRODUCTION

The World Health Organisation recognises asthma as a major health problem[1]. Parents' perception of their child's disease is a significant factor influencing the acceptance of the disease and compliance to therapy. Therefore, patient education programme (PEP) forms an integral component in the long-term management of asthma[2]. Despite the magnitude of the problem, very little is known about the public perception to the diagnosis and the impact of asthma on individuals, their families and communities[3,4]. The objective of the present descriptive study was to evaluate the knowledge, attitude and practice of the parents of asthmatic children about the causation, treatment and prognosis of asthma.

[Received: October 23, 2003; accepted after revision: March 5, 2004]

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MATERIAL AND METHODS

The study was conducted at Chennai City in South India, in two exclusive children's hospitals, namely, Kanchi Kamakoti CHILDS Trust Hospital (KKCTH) and Institute of Child Health and Hospital for Children (ICH & HC). Patients attending the out-patient department, emergency room and pulmonology department were enrolled for the study from June 2001 to September 2001. A diagnosis of asthma was based on history of recurrent reversible bronchospasm responding to bronchodilator drugs.

Children between 2 to 15 years of age having more than four documented episodes of wheeze, with two episodes in the last six months, with at least two emergency room visits and one hospitalisation were enrolled for the study. Children with chronic illness, on therapy for tuberculosis, bronchiectasis, and cardiac diseases were excluded from the analysis. Children who were not accompanied by their parents were also excluded.

An informed consent was obtained from all the participants. A semi-structured pre-validated questionnaire (*see Annexure*) was administered to the parents of these children. The questions were designed to elicit a short answer or response to a multiple-choice format. The parents were asked about their perception of asthma / their child's illness as to what they perceived. The questions dealt with the nature of illness, natural history, aetiology, treatment and prognosis. The parents were asked to identify and describe possible causes of asthma with no limit being placed on the number. The same person (S. Shivbalan) conducted the interview in a separate room with the parents of the child. Each interview lasted for 30 to 40 minutes. No attempt was made to correct a wrong answer or response until the completion of the interview.

RESULTS

A total of 100 cases were enrolled for the study and the interview was completed. Fathers were the respondents in 37 and mothers in the remaining 63. The socio-economic status was assessed as per Gupta's classification[5] (based on per capita income). Majority of the respondents belonged to the middle strata (87%), with most of them living in urban areas (urban 61% semi-urban 26% and rural 13%). Amongst asthmatic children, 61 were boys and 39 were girls, with age ranging from 26 months to 14.5 years. Among the participants 73 were literate (able to read and write a single language with understading) with 27 being illiterate.

Does your child have asthma?

More than a third of the parents responded to the question saying that their children have asthma (39%) and all of them had come to know of the diagnosis through a physician only. The physician was the only source of information regarding the diagnosis and disease related scientific knowledge to these patients. Other responses to this question were wheeze (46%), recurrent respiratory infection (8%), eosinophilia (3%), primary complex (2%), allergy (1%), and respiratory distress (1%).

What do you know about asthma?

Majority of the respondents (54%) were not aware of what asthma is. Asthma as a disease causes difficulty in breathing, due to cold, dust and congestion in the chest was the commonest perception (16%) in those who answered that they were aware of what asthma is. A few (14%) opined that it is a disease of adults, which causes growth retardation and decreased work capability. Only three respondents knew the correct definition of asthma (reversible bronchial obstruction). Other answers, like incurable disease (3%), disease secondary to decreased immunity (2%), tuberculosis (2%), wheezing (2%), contagious disease (2%) and recurrent respiratory infection (1%) were obtained. One of the respondent attributed the illness to be an aftermath of infection acquired antenatally due to ingestion of food substances like citrus fruits and iced drinks by the mother.

Is asthma/their child's illness hereditary?

One-third of the respondents (35%) believed

that asthma is a hereditary disease. Family history of asthma was elicited in 45 percent. Parents of nine children with a family history of wheeze/asthma failed to accept a diagnosis of asthma in their child, despite being informed by the physician, as they considered it to be a disease affecting only adults.

Is asthma/their child's illness contagious?

The perception of asthma as a contagious disease was observed in 26 percent. "Can my younger daughter play and mingle with my son with wheezing" was a common doubt amongst parents. The other opinion elicited in the interview included perception of asthma as air borne disease (20%), water borne disease (3%), due to fomites (7%) and dust (2%).

What caused asthma/their child's illness?

Majority attributed the illness to be due to exposure to various perceived triggers, most of them being dietary items. Dust, cold air (60%) and tobacco smoke (61%) were identified as triggers. Cool drinks, iced water and ice creams were perceived as triggers (68%). Parents also perceived a variety of other triggers as depicted in the table below. Those parents who attributed the asthmatic symptoms to various food substances said that they avoided giving these to their children.

Table. *Percieved triggers by parents of asthmatic children (n=100)*

Perceived triggers	%
Cool drinks	68
Iced water	68
Sweets	44
Exercise	30
Rainy season	29
Chocolates	26
Strong odour	25
Curd	20
Banana	18
Grape	17
Head wash	16
Orange	14
Tomato	10
Cockroaches	10
Animal dander	10

What will you do if your child gets attack of asthma/ their child's illness?

The most common response (62/100) was that they would administer oral beta-agonist medication at home and proceed towards the hospital, with most of them (45/62) using these as cough medications. Visit to the neighbouring physician/hospital was the next common response (20%). Administering of beta-agonist medication using a spacer device at home was reported by eight of the parents interviewed. The other responses elicited included home nebulisation (1%), administration of antibiotics (2%), antihistamines (1%), proprietary topical lozenges/rubefacients medication (5%) and prayer (1%).

Awareness of aerosol therapy ?

All the 100 children had required aerosol therapy of beta-agonist with a nebuliser at least once for control of acute symptoms. Use of nebuliser for therapy was declined by 18% of parents in the out-patient services, saying that it caused nerve weakness because of the vibrations and felt that it should be used only in very sick children. Only 13 children were using aerosol at home. One of the enrolled children was on home nebuliser therapy and the remaining 12 were using spacers (9 on beta-agonist and steroid; 3 on beta-agonist alone). All the parents (n=9) whose children were on aerosol therapy uniformly expressed the opinion that aerosol therapy was addictive and continuous use of medications during symptom free interval will impair their child's ability to outgrow the disease. One of them felt that aerosol therapy increases the symptoms during exacerbations and was giving oral bronchodilators. Forty respondents felt that these devices should be used only in very severe cases, as a last resort. Majority were not aware (47%) that aerosol therapy can be given at home.

Prognosis of asthma/their illness

Once-third of the respondents (34%) thought

that asthma wanes off with increasing age due to increasing immunity and one-fourth felt that the disease was not curable and requires life-long treatment during episodes. The other opinions were: *(i)* asthma is a treatable disease, which decreases in severity with age (19%), *(ii)* asthma is treatable (6%), and *(iii)* it can be controlled (3%). Those who were not aware of the prognosis of the disease (19%) blamed their fate for the suffering of their children.

DISCUSSION

More than half of the population of parents of asthmatic children we interviewed had no real idea about the disease. The diagnosis of asthma was accepted by only 39% of the parents, most of them having a family history of wheeze. The perception of asthma as a disease due to allergy causing narrowing of airways was observed only in 3% of parents interviewed and a few perceived asthma only as an adult oriented disease. Parents easily accepted the diagnosis of asthma if there was a family history of asthma[6]. Inspite of 46 respondents accepting that their children had wheeze, only two of them equated the same with a diagnosis of asthma. The lack of awareness of correct diagnosis is significant, since all children included had recurrent episodes resulting in hospitalisation and emergency room visits. This is a pointer towards the poor asthma awareness prevailing amongst the asthmatic population in Indian children.

In our series, only the physician had disseminated the knowledge of asthma to parents who knew and accepted that their children had asthma. This reinforces the need for the role that can be played by media, non-governmental organisations (NGOs) and health workers in heath education regarding asthma. Formulation of national programmes, conducting continuing medical education (CME) programmes and frequent reminders, such as newsletters, are initial steps in improving asthma knowledge and awareness[7] in the community.

The perception of asthma as a hereditary disease (35%) and as a contagious disease (26%) were other significant observations. The concept of the disease being hereditary and the social stigma attached to the disease hamper the acceptance of the problem in their children. In view of this parents and physicians in particular, intentionally use different entities like 'allergic bronchitis', 'cold allergy' 'chronic bronchitis' to label the disease[2,8]. A previous KAP study in India in the last decade documented almost similar observations[8]. Allergen control helps in improving asthma and reducing the need for medication[2]. In our series the correct identification of triggers like exercise, strong odour, animal dander, cockroach and tobacco smoke[2,9,10] is encouraging. In India 14.8% of asthmatics have been reported to show asthmagenic response on allergic food challenge test[2]. Studies have identified food triggers like grapes (57%), banana (53%), guava (51%), citrus fruits (28%), ice creams (21.5%) and tomatoes (12.5%)[9]. Our series too had similar observations. Similar observations have been made from neighbouring Pakistan and Saudi Arabia, where nutritious foods have been reported as perceived triggers for asthma[11,12]. The cause-effect relationship between triggers and wheeze needs to be further looked into. But the perception that asthma is a disorder precipitated by triggers can be used to our advantage in patient education programmes.

Self-administration of oral beta-agonist for acute symptoms at home was the commonest action plan reported by parents (62%). This is encouraging as it forms a right step toward therapy of acute asthma. An earlier study from India also recorded similar observation that 89.4% of parents either gave bronchodilator at home or consulted a doctor[8]. Even in a developed country like USA only 25% of hospitalised adult patients had written action plan for asthma management[13,14]. In our series, administration of topical proprietary anticold preparations, antibiotics, antihistamine and prayer were other modalities of treatment practiced by patients. None in our study had reported administering corticosteroids by themselves for an acute attack. The observation that only 2% administered antibiotics on their own for acute exacerbation is heartening. The attitude that all

episodes irrespective of severity have to be seen by their physician needs to be changed. It has been earlier reported that patients who did not report a history of asthma were more likely to be treated with antibiotics and anti-tussives in place of drugs indicated for asthma[15].

Very few children (13%) in our study group were on aerosol therapy at home. The notion that these devices are addictive or harmful has lead to the non-acceptance of these modalities of therapy amongst the patients in our series as has been reported earlier[2,4]. Though all children received aerosol through a nebuliser at least once for the control of acute symptoms, acceptance of aerosol therapy overall is poor. It is a common misconception that aerosol therapy is the end to the road[2], and this scenario remains unchanged in our cases. In the management of chronic asthma, patient's acceptance of the disease and compliance to therapy play a major role[7]. It has been observed that parents hesitate to use long-term preventive medications particularly in symptom free interval because they consider asthma to be a series of acute episodes rather than a chronic disease[4]. Parents in the study also held the view that continuous medicines impair the child's ability to outgrow the disease.

Parents held diverse views regarding the prognosis and treatment of asthma. One-third thought that the disease wanes off with age while one-fourth thought that the disease was not curable. The concept of asthma being 'not curable' like tuberculosis or malaria impedes the acceptance of the disease[2]. Few felt that asthma was treatable or controllable reflecting the prevalence of wrong concepts about the disease amongst parents. However, the perception that children outgrow the problem with age by one-third of the parents interviewed is encouraging.

In conclusion, information about asthma has not percolated enough towards parents of asthmatic children in our setting. Misconceptions about the disease and the paucity of information about current trends in management among parents are a significant finding. Asthma management programmes as incomplete without a good tailored patient education programme. Such a programme should augment awareness, eliminate social stigma and misconcepts in the community regarding asthma. Knowledge about the prevailing perception in the community would be the first step in achieving this.

Annexure

Proforma

Name: Date of Birth: Age:
Address: Sex: Hosp. No.:

Literacy of the parent (Respondent):
[Able to read and write a language with understanding]

Rural / Urban / Sub-urban:

Socio-economic status (per capita income):
[Gupta's classification]

Age of onset of wheeze / presenting illness:

Family H/O asthma / similar illness:
Siblings/Parents/Grand parents/Others (cousins/uncle/aunt)

Does your child have asthma?: Y / N
If yes, how did you come to know that your child has asthma?
If no, what disease do you thnik your child has?

What do you know about the disease asthma?

Is asthma / your child's illness, a hereditary disease?

Is asthma / your child's illness, a contagious disease?

What do you think asthma / your child's illness is caused by?

Who is regularly treating your child for asthma / your child's illness?
G.P. / Pulmonologist / Pediatrician / Other's *[specify]*

What will you do if your child develops acute wheezing / breathlessness with cough, at the middle of the night at home?

What measures have you taken so far to prevent asthma / your child's illness?

Who advised you these methods?

What medicines do you have at home for this illness (asthma / your child's illness)?

Which of these factors precipitate asthma / your child's illness?

Tobacco smoke	Y / N
Dust mite *(mattress/pillow/curtain/stuffed toys)*	Y / N
Animal dander	Y / N
Cockroach	Y / N
Indoor mould	Y / N
Pollen / outdoor mould	Y / N
Strong odour (*sprays/perfume/talcum powder)*	Y / N
Other smells	Y / N
Exercise	Y / N
Sports	Y / N
Cold air	Y / N
Medicines	Y / N
Swimming	Y / N
Sulfite in food (*dried fruits/processed potato/sauces*)	Y / N
Any other [*specify in their own words*]	
Do you know about aerosol therpay	Y / N
Is your child on aerosol therapy?	Y / N

If yes, the device used: MDI / MDI + spacer / MDI + spacer + mask DPI / Nebuliser

Who initiated aerosol therapy?
GP / Pulmonologist / Pediatrician / Other's *[specify]*

What aerosol drug is your child been given?
Beta–agonist / Salmeterol / Steroids / Sod. Cromoglycate

Do you think aerosol therapy (MDI / DPI / Nebuliser) is
Addictive: Y / N
Harmful: Y / N

If harmful what are their side effects (*in their own words*)?

How did you come to know about the side effects of aerosol therapy (MDI / DPI / Nebuliser)?

Is your child receiving any regular daily oral medication for more than a month?: Y / N
If yes, what medication?
Advised by whom?

Do you think asthma / your child's illness is curable?

Do you know about peak flow meter? Y / N
If yes, are you using one? Y / N

Any alternative system of medicine attempted? Y / N
If so, details:

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ORIGINAL ARTICLE

Study on Serum and Urinary Cortisol Levels of Asthmatic Patients After Treatment with High Dose Inhaled Beclomethasone Dipropionate or Budesonide

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ABSTRACT

Background. The potential for long-term adverse effects from inhaled corticosteroids relates to their systemic absorption. With increasing use of high dose inhaled corticosteroids, there is need to establish whether similar doses of beclomethasone dipropionate (BDP) and budesonide (BUD) produce clinically important differences in untoward side effects specially hypothalamo-pituitary-adrenal (HPA) axis suppression.

Methods. Fifteen asthmatic patients were started on BDP or BUD (2000 µg / day) through spacer for six weeks. Serum cortisol (9 AM and 4 PM), 24-hour urinary steroid and pulmonary function testing parameters were performed.

Results. The serum cortisol levels were not found to be suppressed with either BDP or BUD. Similarly no significant changes were found in 24 hours urinary excretion of steroids with either of the drugs. Significant improvement was found in values of forced expiratory volume in the first second (FEV_1) with BDP. With BUD the changes in forced vital capacity (FVC) and FEV_1 were found to be significant.

Conclusion. BDP or BUD in high doses of 2000 µg / day given upto six weeks through spacer are equally effective for treatment of bronchial asthma and do not cause any significant change in serum and urinary cortisol levels, and adrenal function / HPA axis.

Key words: *Asthma, Beclomethasone, Budesonide, HPA suppression.*

[Indian J Chest Dis Allied Sci 2005; 47: 89-95]

INTRODUCTION

Bronchial asthma is an airway inflammatory disorder[1]. This has led to the current therapeutic recommendations giving more emphasis on antiinflammatory drugs than bronchodilators. Inhaled corticosteroids (CS) are now well established first line drugs for asthma. Introduction of inhaled corticosteroids in 1972 for the treatment of asthma was an important achievement[2] since these drugs had the potential to replace oral corticosteroids, which

[Received: November 5, 2003; accepted after revision: March 17, 2004]

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were associated with several side effects such as suppression of adrenal functions[3,4]. Several corticosteroids are available for use in inhaled form including beclomethasone dipropionate (BDP), budesonide (BUD), fluticasone and triamcinalone. Although these drugs are considered safe, there is a concern about adverse effects such as suppression of the hypothalamo-pituitary-adrenal axis (HPA axis) especially with high doses. Studies with lower doses (800-1600 μg) of BDP and BUD without spacers have been conducted by various workers for 6-week periods showing variable results[5,6]. Occasionally patients may require doses upto 2000 μg per day, but a systematic study using high dose of BDP or BUD (2000 μg per day) to compare the effect on HPA axis has not been conducted so far[7-9]. Therefore, a 6-week study period was adopted using a double-blind cross-over design for the two corticosteroids and effect on HPA axis was evaluated as reported in this communication.

MATERIAL AND METHODS

Subjects

Fifteen newly diagnosed patients with asthma of either sex were recruited from the Clinical Research Centre, V.P. Chest Institute for the study. The patient characteristics are presented in table 1. The study was approved by the Institutional Ethics Committee. A written informed consent was taken from all the patients. The diagnosis was based on history of recurrent cough and wheezing and documentation of a greater than 12% and 200 ml increase in the ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) after inhalation of 200 μg inhaled salbutamol. Patients of either sex, aged between 14 to 45 years were included in the study. They were non-smokers and did not have any other systemic disease. Pulmonary function testing was performed on computerized lung function apparatus (Morgan transfer test, Model C, Kent, England) to measure FVC and FEV_1. Chest radiograph and haemogram were also obtained. The study also included ten healthy subjects of either sex, age ranging between 18 to 35 years to establish the normal range of serum and urinary cortisol. They did not have history of any respiratory or systemic illness, were non-smokers and were not taking any medication.

Table 1. *Patients characteristics*

	Patients (n=15) mean ± SD	**Normal (n=10)** mean ± SD
Age (yrs)	28.6±8.0	27.8±6.4
Sex		
Males	14	8
Females	1	2
Height (cm)	160.4±6.7	158.2±5.3
Weight (kg)	51.2±9.0	52.3±5.8

Study design

The study was carried out in the out-patient setting. After a run in period of one week, a double-blind randomised cross-over design was adopted. Patients were started on either inhaled BDP (Beclate – Cipla) or BUD (Budecort – Cipla) at a dosage of 2000 μg per day in two divided doses given through a spacer for six weeks. This was followed by a wash-out period of one week following which other treatment was given for another six weeks. The two treatments were labelled as 'Treatment 1 (BDP)' and 'Treatment 2 (BUD)'. Whether a patient would start with treatment 1 or 2, was decided by computer generated random numbers. All patients were given salbutamol inhaler (100 μg per puff – Asthalin – Cipla) to be taken on an as-needed basis throughout the study. A record of symptoms and drugs used by the patient was maintained. The patients were trained on how to fill the diary during the run in period. Samples of blood and urine were collected at the beginning and at the end of both the treatment periods. Outcome parameters that were studied before and after each treatment period consisted of serum cortisol, urinary cortisol and spirometry (FVC, FEV_1).

Collection of blood and urine samples

The investigations were carried out after admitting the patients for a day. The treatment

was then continued at home. Patients were admitted in the ward of the Clinical Research Centre, V.P. Chest Institute for sample collection. Blood samples (5 ml) were withdrawn at 9 AM and 4 PM, allowed to clot, and centrifuged at 2000 rpm for 30 minutes for serum separation. Supernatant serum sample was stored in micro centrifuge tube at –20 °C in a deep freezer until analysis. For collection of urine, patients were explained to empty the bladder before the start of experiments and all the urinary fractions upto 24 hours collected. The urinary volume was measured and suitable aliquots preserved and analysed for cortisol estimation.

Determination of serum 11-hydroxy corticosteroid

Serum cortisol level was determined by the fluorometric method as described by Mattingly[10]. To 0.5 ml of serum in a glass stoppered tube, 0.5 ml of distilled water was added. This was followed by addition of 7.5 ml of methylene chloride (MC). The tube was stoppered and shaken slowly for 20 min to extract the steroid. The phases were allowed to settle and supernatant aqueous layer was pipetted out and discarded. A blank containing 1 ml distilled water and a standard containing 0.5 µl of steroid were similarly processed (10 mg of hydrocortisone was dissolved in 10 ml of ethanol; 100 µl of this solution was diluted in 100 ml of distilled water to make the working standards).

At zero time, 5 ml of MC extract from the 'blank' was added to 2.5 ml of fluorescent reagent (prepared by mixing 7 volumes of concentrated sulphuric acid to 3 volumes of ethanol) in a clean dry glass stoppered tube. It was shaken vigorously for 20 seconds. This procedure was repeated at one minute intervals, using MC extract from 'standard' tube next followed by extract from the 'test'. The MC layer was pipetted out, discarded from each tube and the acid extracts transferred to glass cuvettes 13 minutes after mixing the MC extract. The fluorescence was read in a spectrofluorometer (model RF 5000 Shimadzu) at 540 nm was read with excitation wavelength at 430 nm. Serum cortisol level was calculated by the following formula:

$$\text{Serum-11-hydroxy corticosteroid} = \left(\frac{T}{S}\right) \times 100\ \mu g / 100\ ml$$

where T is the fluorescence of 'test' and S is the fluorescence of 'Standard'.

Determination of urinary 17-oxogenic steroids

Urinary steroid was measured by spectrophotometric method of Mattingly[10]. To 4 ml of urine sample in a screw capped tube (test), 20 mg of potassium borohydride was added which was left open overnight at room temperature. Then 4 ml of glacial acetic acid was added followed by 1 g of sodium bismuthate. The tube was shaken for 30 minutes in dark and centrifuged for 10 minutes at 2000 rpm. The supernatant was collected and 5 ml of it transferred to a clean glass stoppered tube. Then 0.1 ml of 20% sodium metabisulphite was added to decolourise the sample and the contents were diluted with 5 ml of water. This was followed by addition of 1 ml of conc. hydrochloric acid. The tube was then heated in a boiling water bath for 20 minutes, cooled and 10 ml of chloroform added. The steroid was extracted into the chloroform by vigorous shaking. The chloroform extract was washed with 3 ml of 1 N sodium hydroxide solution and washed twice with 3 ml of water. Of this washed chloroform extract, 6 ml was taken in a clean dry test tube. The chloroform was evaporated to dryness by warming the tube in a hot water bath. The dried residue contained steroid from 1.5 ml of urine.

'Standard' (200 µl) containing 0.2 µg steroid was taken in a similar test tube and evaporated to dryness (standard solution was prepared by adding 10 mg of dehydroepiandrosterone per 100 ml in ethanol). A clean test tube served as 'blank'. To test, standard and blank, 0.25 ml of freshly prepared Zimmerman reagent (equal volumes of m-dinitrobenzene solution and 40% benzyltrimethyl-ammonium-hydroxide were mixed to form Zimmerman reagent. Meta-dinitrobenzene solution was prepared by dissolving 1g per 100 ml ethanol). The tubes were allowed to stand in dark for one hour. Then 3 ml ethanol was added to each tube and mixed well. The extinction of test and standard was measured at 440, 520 and 600 nm. In each

case blank was used to set the instrument to zero. For test and standard, a corrected extinction (Ecorr) was measured on spectrophotometer (model Bousch and Lomb, Spectronic 21) by the following relation.

$$Ecorr = E_{520} - \frac{1}{2} \quad (E_{440} + E_{600})$$

The amount of steroid in the sample was calculated as follows:

$$\text{Steroid excretion (mg per 24 hours)} = \frac{\text{Ecorr for 'test'}}{\text{Ecorr for standard}} \times \frac{V}{75}$$

where V is the volume of urine excreted in 24 hours.

Statistical analysis

Student's 't' test for paired samples was applied for statistical analysis; $p<0.05$ was considered significant.

RESULTS

Only 13 of the 15 patients completed the study as scheduled. One patient opted out of the study during the second drug phase and other during the first drug phase. Therefore the statistical analysis was performed using the data of 13 patients only.

Serum and urinary steroid levels of normal subjects

The normal ranges were established by estimating the serum cortisol (9 AM and 4 PM) and 24 hours urinary steroid levels in 10 healthy subjects. The data suggests the normal range for serum cortisol at 9 AM to be 10.60 – 26.29 µg / 100 ml (mean ± SD 17.61 ± 4.81) and at 4 PM to be 6.66 – 15.43 µg / 100 ml (mean ± SD 8.92 ± 2.26). In 24 hours urinary samples, the steroid level was 7.26 – 22.04 mg / 24 hours (mean ± SD 15.14 ± 4.87).

Effect of BDP and BUD treatment on cortisol levels in asthmatics

The mean changes in cortisol levels in the serum and urine before and after treatment with BDP and BUD are given in table 2. The mean values of serum cortisol at 9 AM showed a slight fall on giving BUD and a slight rise on giving BDP, which were not significant. The absolute as well as the mean values of serum cortisol (9 AM and 4 PM) of all patients were found to be within normal range after treatment with either BDP or BUD. Similarly, the mean serum cortisol values at 4 PM after BDP treatment showed a slight fall, which was also observed on treatment with BUD. These changes were also not found to be statistically significant. With both BDP and BUD, there was a slight fall in the values of 24 hours urinary steroid. However, this change was not found to be statistically significant. The absolute as well as the mean values of all patients after either of the drugs was found to be within the normal range.

Table 2. *Serum and urinary cortisol levels and pulmonary functions parameters before and after treatment with beclomethasone dipropionate or budesonide* (mean ± SD)*

	BDP n=13		**BUD n=13**	
	0 Week	6th Week	0 Week	6th Week
Serum cortisol (9 AM) µg per 100 ml	19.27 ± 4.41	19.67 ± 4.10	19.63 ± 3.58	18.78 ± 3.26
Serum cortisol (4 PM) µg per 100 ml	12.46 ± 2.95	12.42 ± 2.73	12.53 ± 2.03	11.57 ± 2.35
24 hr urinary steroids mg / 24 hours	16.20 ± 4.92	15.80 ± 3.73	15.63 ± 4.02	15.49 ± 3.19
FVC (L)	2.89 ± 0.80	3.04 ± 0.87	3.18 ± 0.72	3.71 ± 0.62†
FEV_1 (L)	1.86 ± 0.88	2.44 ± 0.76†	2.14 ± 0.79	2.69 ± 0.82†

* All values expressed as mean ± SD, †P<0.05,
BDP– beclomethasone dipropionate, BUD– budesonide.

The individual patient data was analysed to look for the percentage of patients showing greater than 20% change in values of various parameters. The data of serum cortisol at 9 AM showed that after treatment with BDP, there was a fall by greater than 20 % in four patients (31%). With BUD, three patients (23%) showed, greater than 20% fall. However, on applying Chi square test it was not found to be significant ($p>0.5$). The serum cortisol level at 4 PM showed greater than 20% fall after treatment with BDP in four patients (31%), while six patients (46%) showed greater than 20% fall in their values after BUD ($p>0.1$). The value of 24 hours urinary cortisol excretion indicates that after treatment with BDP, there was a fall of greater than 20% in five patients (39%). Following treatment with BUD, fall was seen in three patients (23%) ($p>0.1$).

Effect of BDP and BUD on pulmonary function tests before and after treatment

Table 2 summarises the changes in the various parameters of pulmonary function tests. There was a significant ($p<0.05$) rise in the value of FVC as compared to baseline in patients who received BUD. The change in FVC after BDP was however not found to be significant. With BDP the mean increase was 180 ml while with BUD it was 530 ml. A significant ($p<0.05$) increase was observed in the values of FEV_1 after treatment with BDP or BUD. Similarly treatment with either BDP or BUD produced a significant ($p<0.05$) rise in forced expiratory flow between 25% and 75% of the vital capacity (FEF_{25-75}). The values of peak expiratory flow rate (PEFR) showed a slight fall after BDP treatment. The treatment with BUD, however caused an increase in the value of PEFR which was statistically insignificant.

Further, the analysis of the individual patient data revealed that three patients (23%) showed greater than 20% improvement in FVC with both BUD and BDP. Similarly six patients (46%) showed an improvement in FEV_1 with both BDP and BUD. Five patients (39%) receiving BDP and three patients (23%) receiving BUD showed greater than 20% improvement in FEV_1/FVC. An improvement of greater than 20% in FEF_{25-75} was apparent in seven patients (54%) with both the drugs. The PEFR improved by greater than 20% after treatment in three patients (23%) with BDP and five patients (39%) with BUD.

DISCUSSION

Both BDP and BUD resulted in improvement in lung functions. With BUD, a greater improvement was observed in FVC, while the change in FEV_1 was similar with both. Several studies have been performed till date with BDP and BUD for 6-week period[5,6,11] but they did not use spacers while studying adrenal function. Very few studies have been done in this aspect[5,12]. In the present study, serum steroid levels were not found to be suppressed with either BDP or BUD. Similarly no significant changes were found in 24 hours urinary excretion of steroids with either of the drugs.

The effect of inhaled high dose CS on HPA axis is related to the degree of its systemic absorption. About 10% of steroid delivered by metered dose inhalers (MDI) reaches the lower airway[13,14]. Orally administered BDP causes considerably less HPA axis suppression than oral dexamethasone because of extensive hepatic metabolism of BDP to inactive polar metabolites, whereas after dexamethasone upto 80% of the circulating drug is unchanged[15]. Studies in animal models[13] and in man[14] show that spacers provide more selective delivery of inhaled CS to the lung. With large spacing devices, the proportion of steroid deposited on the oropharynx decreased to 10% of the delivered dose and the fraction deposited in the lungs was maintained or even increased. About 40% of the delivered dose remains in the spacing device[13,14]. Spacers therefore increase the steroid dose supplied to the lower airway and reduce HPA axis suppression caused by the systemic absorption of steroid from the mouth, oropharynx and gut.

A study in children had shown that adding a spacing device to a MDI increased 24 hours urinary steroid excretion, implying improved adrenocortical functions[16]. Farrer *et al*[17] studied the effect of 750 ml spacing device on morning

serum cortisol concentrations after 2000 µg inhaled BDP in normal subjects. They concluded that a spacing device attached to MDI may decrease the rate of HPA axis suppression by high dose inhaled steroid treatment. But in their study[17], a single dose of CS was given to normal individuals, which does not address to questions of safety and efficacy in asthmatic patients, who use inhaled steroids regularly. In the present study, absence of any suppressive effects on adrenal functions of inhaled BDP and BUD regularly for six weeks can be attributed to the use of the spacer device throughout the study period.

Ebden *et al*[6] compared BDP (1500 µg / day) and BUD (1600 µg / day) for chronic asthma. They used spacers only with BUD. There was no significant difference in the control of asthma during the two treatment periods. There was no significant difference in FEV_1 and FVC or in mean morning and evening peak expiratory flow rates. The mean basal cortisol concentrations were significantly lower with both the drugs but there was no significant difference between the mean basal cortisol values of these drugs. In their study, the dosage used was not identical, and spacers were not used in all the patients. Boe *et al*[18] who used 1600 µg BDP and 2000 µg fluticasone propionate did not find suppression of HPA axis with BDP.

Svendsen *et al*[5] gave BDP (1500 µg / day) and BUD (1600 µg/day) to asthmatic patients alternatively for six weeks through MDI. Spacers were not used. They concluded that inhalation of BUD and BDP in high dose are equally potent in the treatment of severe asthma and that there was no significant influence on adrenal functions and no significant side effects. Our results are also in agreement with their findings, though we used a higher dosage.

In a study on nine healthy subjects by Brown *et al*[12], systemic effects of high dose inhaled BDP and BUD were compared. Spacer was used for BDP and nebuhaler for BUD. They found that BDP inhaled without a spacer reduced urinary steroid and plasma osteocalcin in 24 hours; however the use of a spacer protects against these effects. Attaching a spacer reduces the systemic effects of 2000 µg / day BDP on HPA axis and circulating osteocalcin concentration. Their study did not establish whether nebuhaler reduces the systemic effects of BUD. When large volume spacers are used, 2000 µg / day of BDP and BUD seem to be equivalent in terms of unwanted effects.

Grebe *et al*[19] conducted a study on non specialist clinic asthma patients on moderate to large doses of inhaled BDP and they concluded that there appears no 'safe' threshold, and around 15% patients may have clinically significant HPA axis suppression.

A study done by Aaronson *et al*[20] on BUD inhaled by a turbohaler at doses recommended for clinical use (800 or 1600 µg / day) concluded that no HPA axis suppression was produced as compared to placebo. Andersson *et al*[7] found non-suppression of HPA axis with 400 µg/day dose of BUD but 800 µg/day dose resulted in statistically significant suppression of HPA axis. Ninan *et al*[21] concluded in their study done on children that adrenal suppression occurs in some children who are given inhaled BUD and BDP in doses greater than 400 µg / day. Irani *et al*[8] who conducted a study on infants and young children indicated that treatment with BUD inhalation does not result in clinically significant suppression of HPA axis. These doses were much lower than the doses used in our study.

In the present study we followed a uniform pattern in terms of dose and use of spacer. The analysis of results did not show any significant difference between the mean values of the serum and urinary steroid levels after treatment with these drugs at 2000 µg/day for six weeks suggesting no suppression of adrenal function. Thus, they are effective and safe as high dose inhalation therapy with spacers for treatment of bronchial asthma for a period of at least six weeks.

We conclude that treatment of asthmatic patients with high dose (2000 µg/day) inhaled BDP or BUD for six weeks, given through spacer, did not change serum steroid levels, and their 24 hours urinary excretion, suggesting no significant effect on adrenal functions / HPA

axis. However, the treatment with BDP significantly improved FEV_1 while treatment with BUD significantly changed both FVC and FEV_1, showing a significant improvement in lung function.

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Editor-in-Chief

Acute Lower Respiratory Tract Infection due to *Chlamydia* Species in Children Under Five Years of Age

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ABSTRACT

Background. The contribution of *Chlamydia* spp in respiratory tract infections in paediatric population from India has not been studied in detail.

Methods. Sixty children under five years of age who were admitted with acute lower respiratory tract infection during a one year period were investigated for Chlamydial aetiology of respiratory infection. Diagnosis was based on antigen detection by direct immuno-fluorescence (DIF) in throat swab along with anti-Chlamydial immunoglobulin G (IgG) antibody demonstration by solid phase enzyme immunoassay (EIA).

Results. *Chlamydia* spp antigen was detected in seven (11.6%) cases, *C. pneumoniae* in six (10%) and *C. trachomatis* in one (1.6%). *Chlamydia* spp IgG antibody in serum was demonstrated in 24 (40%) cases, of which *C. pneumoniae* IgG was denconstrated in 18 (30%) cases. Taking the criteria of antigen detection (n=7) and high IgG antibody titre of ≥1: 512 (n=5) for a positive case, 12 (20%) children were found to be suffering from recent Chlamydial infection.

Conclusion. *Chlamydia* spp plays a significant role in respiratory tract infections in Indian paediatric population. Diagnostic procedure like antigen detection in throat swab is rapid, less cumbersome and feasible and should be more widely used along with antibody demonstration to determine the aetiological agent early in the course of illness.

Key words: *C. pneumoniae, Antigen detection, Acute lower respiratory tract infection.*

[Indian J Chest Dis Allied Sci 2005; 47: 97-101

INTRODUCTION

Acute lower respiratory tract infection (ALRTI) is the major cause of morbidity and mortality in young children world-wide[1]. *Chlamydia pneumoniae* is a common respiratory pathogen which is responsible for about 10% of community acquired pneumonia (CAP)[2]. The best method of microbiological diagnosis at the acute stage of Chlamydial infection is undecided, because the organism grows poorly on cell culture[2] and tests like polymerase chain reaction (PCR)[3] are not widely available. Antigen detection by direct immuno-fluorescence (DIF) and antibody demonstration by enzyme immunoassay (EIA) are the other tests which are rapid, technically less demanding and suitable for the routine laboratories[4,5]. Role of *Chlamydia* spp as a causative agent of ALRTI in Indian children is not known. Prevalence of

[Received: July 8, 2003; accepted after revision: February 16, 2004]

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Chlamydia in children was determined by serology using EIA and indirect immunofluorescence assay (IFA) in some studies[6,7]. The present study was undertaken to diagnose Chlamydial infection in children under five years of age with ALRTI by antigen detection in throat swab using DIF in addition to serology, so as to determine the infective aetiology early in the course of illness, which will help towards better management and treatment of these cases.

MATERIAL AND METHODS

Study Population

The study population comprised of 60 children of either gender and under five years of age, admitted to all India Institute Medical Sciences, New Delhi, India, with complaints suggestive of acute lower respiratory tract infection (ALRTI). A child was considered as having ALRTI if he or she had at least three of the following signs and symptoms: cough, fever, difficulty in breathing, wheezing, breathlessness of less than two weeks duration with chest radiograph showing evidence of pneumonia (WHO)[8]. Children below six months of age and children who had received antibiotics and/or were on immuno-suppressive drugs were excluded from the study. Thirty children under five years of age who were admitted to the hospital but without evidence of any respiratory or cardiac disease were included as controls. Informed consent from the parents was taken before collecting the specimen.

Specimens

Throat swabs were collected from all the patients and the controls for antigen detection of *Chlamydia* spp using direct immunofluorescence (DIF). The swabs were accepted only if squamous epithelial cells were seen on DIF microscopy. The swabs were also cultured to look for other bacterial etiology of ALRTI. In addition to this, blood samples were obtained for serology of *Chlamydia*. The sera was separated and stored at –20 ^{0}C until tested.

DIF method for throat swabs. Chlamydia spp antigen was detected by DIF in throat swab using Chlamydia Cel Bivalent IF kit (Cellabs Diagnostics, New South Wales, Australia)[9,10]. This kit employs a type specific monoclonal immunoglobulin M (IgM) antibody for *C. pneumoniae* and *C. trachomatis* detection. The antigen detected is the species specific outer membrance protein (OMP). A 5 ml aliquot of *C. pneumoniae* or *C. trachomatis* monoclonal antibody supplied with the kit was added to each specimen well, previously coated with throat swab. Slides were incubated in a moist chamber at 37 ^{0}C for 30 minutes, and then washed in phosphate buffered saline (PBS), pH 7.4, for approximately one minute. Anti-mouse Ig-FITC reagent was then added to each well. The slide was incubated in a moist chamber in dark at 37 ^{o}C, washed in PBS, and a drop of mounting fluid added to the slide before applying a cover slip and then examined by fluorescence microscopy with an oil immersion lens at × 600 and × 1000 magnification. The control slide was used to check the morphology of these elementary bodies (EB). A test was taken as positive when four or more EB appearing as bright apple-green fluorescent disc shaped bodies about 300 nm in diameter were seen. Positive and negative control slides were included in each test run.

Antibody Detection

All the serum samples were tested for IgG antibody against *Chlamydia* spp using solid phase enzyme immunoassay, the Immunocomb Chlamydia Bivalent IgG kit (PBS Organics, Cedex). This assay provides differential detection and quantitation of specific IgG antibody against *C. pneumoniae* and *C. trachomatis*. The lower cut-off for positive antibody titre was ≥1:16 which indicates past infection[11]. Single serum samples were tested in each patient and control, and only a high titre of ≥ 1:512 was considered as positive for recent Chlamydial infections[11]. Criteria taken for recent acute infection was: *(i)* presence of Chlamydial antigen in throat swab and/or *(ii)* presence of high IgG antibody titre of ≥1:512 in single serum sample.

RESULTS

Tachypnoea or difficulty in breathing constituted the main criterion present in all the study population. Fever (57.1%) and cough (48.5%) were the other predominant symptoms. Of the total 60 patients from whom throat swab specimens were received, seven (11.6%) were positive for Chlamydial antigen. Of these, six (10%) were positive for *C. pneumoniae* and one (1.6%) for *C. trachomatis*. Chlamydial antigen was not detected in any of the 30 controls.

Anti Chlamydial IgG antibodies could be demonstrated in 24 (40%) patients and four (13.3%) control. Of the 24 cases, 18 (30%) were positive for anti *C. pneumoniae* antibodies, one (1.6%) for anti *C. trachomatis* antibodies and in five (8.3%) cases IgG antibodies were demonstrated against both *C. pneumoniae* and *C. trachomatis*. Five of the cases positive for anti *C. pneumoniae* IgG antibodies showed high titres of ≥ 1:512. All the seven Chlamydial antigen positive cases were also sero-positive for anti Chlamydial IgG (*see table*).

In the present study along with *Chlamydia* spp, other aetiologies of ALRTI were also looked for. It was observed that *Chlamydia pneumoniae* besides presenting as a sole pathogen also occurred as mixed infection in five (8.2%) cases. Two of these cases showed co-infection with *Streptococcus pneumoniae*, two with *Staphylococcus aureus* and one with *Mycoplasma pneumoniae*.

DISCUSSION

Evidence of the role of *Chlamydia* spp as a causative agent of ALRTI in Indian children is ambiguous. Careful search of the literature has shown limited reports on respiratory tract infection in children from India[12-15]. However, these studies have not looked for role of *Chlamydia* spp in ALTRI. Sero-prevalence of Chlamydial infection has been studied by two groups of workers from India, where Chlamydial IgG antibody was demonstrated by EIA and IFA, respectively[6,7]. To the best of our knowledge, the present study is the first of its kind from India in which an additional effort was made to diagnose *Chlamydial* infection in children with ALRTI by direct antigen detection in throat in addition to serology.

In our study, 24 patients were positive for anti Chlamydia IgG antibodies. Of these, 19 patients showed a titre of ≥ 1:16 which is indicative of past infection and five samples showed IgG antibody titre of ≥1:512 indicating recent *C. pneumoniae* infection. None of the control children in our study showed IgG antibody titre of ≥ 1:512. These cut-off titres were first suggested by Grayston *et al*[11] in 1989 and since then have been used by various authors [16, 17]. Taking antigen detection (7/60) and/or high IgG antibody titre ≥1:512 (5/60) as evidence of infection, a total of 12/60 (20%) children in the present study were suffering from recent Chlamydial infection, but none in the controls. Our finding of Chlamydial infec-

Table. *Results of various methods used to detect Chlamydia spp*

Type of Test	Number of Positive Samples (%)	
	Patient group	**Control group**
EIA for antibody detection (≥1:16)		
C. pneumoniae	18 (30%)*	4 (13.3%)
C. trachomatis	1 (1.6%)	nil
Both *C. pneumoniae* and *C. trachomatis*	5 (8.3%)	nil
DIF for antigen detection		
C. pneumoniae	6 (8.3%)	nil
C. trachomatis	1 (1.6%)	nil

*Five cases showed titres of ≥ 1:512; EIA = Enzyme immunoassay; DIF = Direct immunofluorescence

tion in 20% of cases is significant. Garnett *et al*[10] had reported *C. pneumoniae* in 36% cases of lower respiratory tract infection, which was unexpectedly high. According to the authros, the possibility of local epidemic at the time of the study cannot be ruled out. Mixed infections were detected in 8.2% of *C. pneumoniae* positive samples. This implies that the detection of easily cultivable bacteria in a sample should not stop further investigation of the patient for other atypical pathogens. This in turn would also prevent false labelling of the isolates to be resistant *in vivo*.

No method for detection of *Chlamydia* in routine microbiology is ideal. Culture is cumbersome as well as time consuming and PCR is sensitive and specific but is a specialised method requiring expertise[3]. An alternative method is direct detection of *Chlamydia* from throat swab, as attempted in the present study. Throat swab has advantage over sputum because it is non-invasive, easy to collect and process, particularly in small children where sputum samples cannot be obtained and naso-pharyngeal aspirate may be difficult to collect. Garnett *et al* have evaluated the comparison between throat swab and sputum for Chlamydial antigen detection in respiratory infections using the same antigen detection kit as used by us and have found throat swab as a better and easy alternative[10]. It is also clear from the present study that *C. trachomatis* antibody was detected only in one patient, so the role of *C. trachomatis* in ALRTI is difficult to comment. Singh *et al*[7] have reported *C. trachomat*is IgG antibodies in 0.46% of children less than five years of age.

Demonstration of anti *Chlamydia* IgM antibody along with detection of Chlamydial antigen would have been ideal for diagnosis of recent Chlamydial infection. However, IgM antibody demonstration could not be attempted due to limited resources in the present study. We also did not look for *C. psittacii* as none of our patients and/or control population gave history of contact with animals.

To conclude, first, this study confirms that *C. pneumoniae* plays a significant role in ALRTI in Indian children and to determine the infective aetiology early in the course of illness and methods like DIF and EIA can be employed as these are rapid, feasible, less time consuming and help in better treatment and management. Secondly, further studies with large number of patients are required to find out whether *C. trachomatis* actually plays a role in ALRTI or is it just a coloniser of the throat.

ACKNOWLEDGEMENTS

Authors would like to thank Mr Salek Chand and Ms Puspha for their technical assistance.

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The Indian Association for Bronchology has set up a website and the URL of this site is **www.iabronchology.org**. This website was conceived and started by Dr Sandhya Nanjundiah, past President of the Indian Association for Bronchology. Members of the Indian Association for Bronchology and others interested in Bronchology are requested to contribute scientific articles including case reports to this website. The articles submitted will be peer reviewed by the experts before putting them on the website. The contributors are requested to send the articles to Dr Sandhya Nanjundiah at the following address:

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ORIGINAL ARTICLE

Impact of Vascular Abnormalities in Neoplastic and Non-neoplastic Lung Disease

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ABSTRACT

Background. Vascular abnormalities of the pulmonary circulation in the setting of destructive lung diseases caused by inflammation or neoplasia has been scantily researched. A need was felt to document the spectrum of pathological alterations in the vasculature and thus permit speculation into both their pathogenesis and possible clinical significance.

Methods. Between January 1999 and June 2001, 21 patients (male : female 3 : 4) who had chest disease exceeding a duration of six months and later underwent lobectomy were included in the study. The histopathological material was analysed for vascular changes such as arterial intimal fibrosis, muscularisation of intima and pericapillary fibrosis. The study included a detailed morphometric analysis.

Results. The lesions included 15 non-neoplastic diseases and six neoplastic diseases. The striking vasculopathic changes observed in the absence of pulmonary hypertension were pulmonary artery medial hypertropy (100%), intimal fibrosis (62%) and muscularisation of the neo-intima (3%). Pericapillary fibrosis was seen in 83% of the neoplastic lesions and 67% of the non-neoplastic lesions.

Conclusions. This study highlights the impact of chronic lung disease on pulmonary vasculature. The role that neoplastic and non-neoplastic lung disease have to play in the evolution of the documented vascular changes have been postulated, and the need to design effective therapeutic strategies to modulate hypoxia, reverse the inflammatory process and stabilise the fibroblastic process is also highlighted.

Key words: *Vascular, Lung disease, Morphometry, Pathology.*

[Indian J Chest Dis Allied Sci 2005; 47: 103-107]

INTRODUCTION

Pulmonary vasculopathy in the setting of long standing inflammation and neoplasia has been scarcely researched[1]. Inflammatory and neoplastic lung diseases elaborate chemical and biological products which could have far reaching effects on the morphology and function of vasculature in adjacent uninvolved pulmonic regions. This study aims to document the spectrum of these vascular changes and speculate into their pathogenesis and possible clinical significance.

MATERIAL AND METHODS

We reviewed all the cases of inflammatory

[Received: January 28, 2004; accepted after revision: June 8, 2004]

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and neoplastic lung disease where patients had a documented duration of disease exceeding six months and had undergone lobectomy or total pneumonectomy between January 1999 and June 2001. Twenty-one cases (male : female 3 : 4) fulfilled the criteria and had available tissue sections for detailed morphometric analysis of a minimum of 10 muscular arteries. Case charts, electrocardiogram and echocardiogram reports, chest radiography and pulmonary function tests, wherever available were reviewed to exclude those cases with concomitant pulmonary hypertension.

Five micron sections from the lesional and nonlesional tissue blocks were studied. Sections from nonlesional blocks were stained with haematoxylin and eosin and Verhoeff's elastic stain and examined for vascular changes, using a microscope equipped with a Leitz ocular morphometer. Masson Trichrome was utilised when required. Blood vessels were categorised into capillaries, veins and muscular arteries. Muscular arteries were defined as those whose external diameter ranged between 100 to 1000 microns[2].

In the muscular arteries, the percentage medial thickness which is expressed in relation to the vessels external diameter was calculated in a minimum of 10 muscular arteries. The mean percentage medial thickness was obtained by dividing the sum total of all percentage medial thickness in each case by the number of blood vessels examined in each case. Any value in excess of 10% was considered elevated[2]. Pulmonary arterial medial hypertrophy (PAMH) was further categorised as mild (10% to 40%), moderate (40% to 70%) and severe (≥ 70%). Slides were examined for pulmonary arterial intimal fibrosis, muscularisation of intima, pericapillary fibrosis and neural hypertrophy.

RESULTS

The patients ranged in the age group from 2 to 55 years. The lesions included 15 non-neoplastic diseases comprising lung abscess (n=4), bronchiectasis (n=3), tuberculosis (n=3), aspergillosis (n=1) and hydatid cyst (n=1). Six neoplastic lesions fulfilled the inclusion criteria and included three cases of carcinoid and one each of squamous cell carcinoma, carcinosarcoma and hemangiopericytoma. The changes in blood vessels are presented in the table. Statistical analysis of the data was limited in significance in view of the occurrence of "zero" in five categories. When the data was broadly grouped, Fischer's exact test of statistics was applied to evaluate the pathological abnormalities in the neoplastic and non-neoplastic categories. Both groups showed a similar pattern of vascular abnormalities (with a 2 tailed p value of 1.00 for increased percentage of medial thickness of muscular arteries; 2 tailed p value of 0.52 for intimal hyperplasia and fibrosis and 2 tailed p value of 0.6 for pericapillary fibrosis).

Table. *Spectrum of vascular abnormalities in neoplastic and non-neoplastic pulmonary lesions*

Pathological Abnormalities of Vasculature	Neoplastic No., n = 6 (%)	Non-neoplastic No., n = 15 (%)
Increased percentage medial thickness of muscular arteries		
Marked	0	2 (13)
Moderate	6 (100)	12 (80)
Mild	0	1 (7)
Muscularisation of intima	0	3 (20)
Intimal hyperplasia and fibrosis	3 (50)	10 (66)
Pericapillary fibrosis		
Marked	0	1 (7)
Moderate	4 (67)	0
Mild	1 (17)	9 (60)

Pulmonary arterial medial hypertrophy was a universal finding, with average values ranging from 40 to 68 percent. While the non- neoplastic lesions expressed a range of changes from mild to marked medial hypertrophy, all the neoplastic lesions were associated with a moderate increase in medial fibrosis. Muscularisation of the intima which was best appreciated on sections stained with Masson trichrome was documented in only three cases, all of which were non-neoplastic and 62% showed intimal fibrosis with a predominance of the eccentric pattern of intimal proliferation (Figure 1). Pericapillary fibrosis (Figure 2) characterised by fibroblastic proliferation around vascular channels was seen in 83% of the neoplastic lesions and 67% of the non-neoplastic lesions. Dense conspicuous perivascular infiltration by inflammatory cells was a feature peculiar to the non- neoplastic lesions excepting for the solitary case of carcinosarcoma (Figure 3).

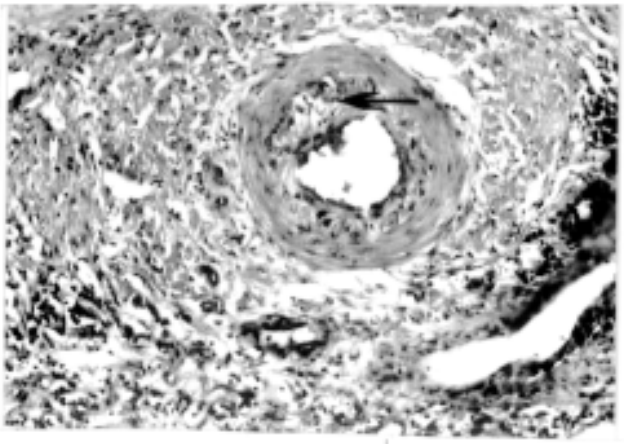

Figure 1. Photomicrograph showing a muscular pulmonary artery exhibiting an eccentric pattern of intimal fibrosis (arrow) (H&E×250).

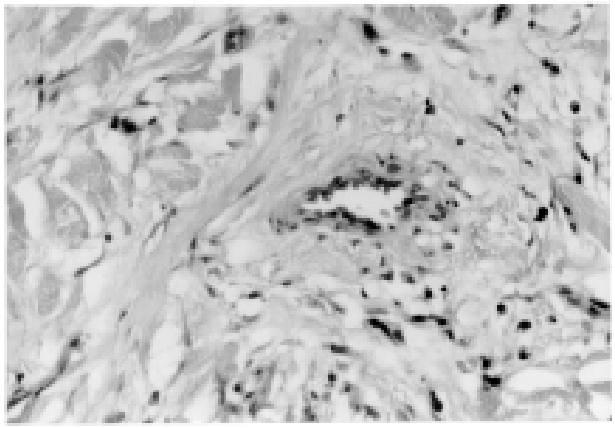

Figure 2. Photomicrograph showing pericapillary fibrosis characterised by fibroblastic proliferation around the vessel wall (H&E×250).

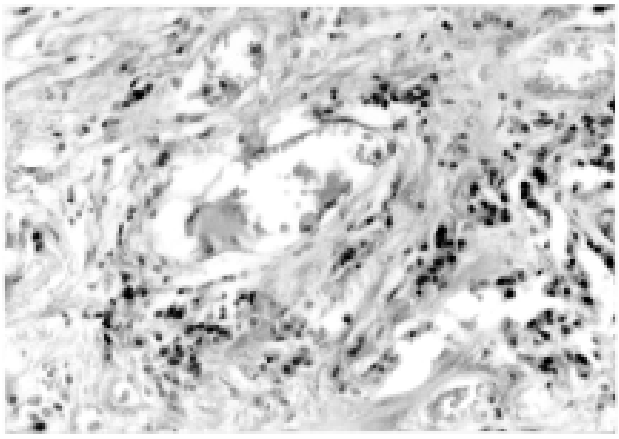

Figure 3. Photomicrograph showing moderately dense infiltrate of chronic inflammatory cells around the capillary wall (H&E×250).

DISCUSSION

This study highlights the impact of chronic lung disease on pulmonary vasculature. Pulmonary vasculopathy was identified in all 21 of our cases. Similar structural changes were documented in a group of 15 patients with chronic obstructive pulmonary disease, who were studied by Zhang *et al*[3]. However, pulmonary hypertension was distinctly absent in all the 21 cases in our study.

Heath and Edwards[2] categorise vascular changes of medial hypertrophy with and without intimal hyperplasia and intimal fibrosis as the early histological phases of pulmonary hypertension. Cyr *et al*[4] observed that PAMH and intimal fibrosis were common findings in resected lung tissue from 20 patients with idiopathic spontaneous pneumothorax who had no evidence of pulmonary hypertension. They attributed the vascular lesions to inflammation and fibrosis in the adjacent lung and observed that they were not of clinical significance, bearing no implication of hypertensive pulmonary vascular disease.

The documented changes of the intima and media may have been catalysed by endothelial damage. Abcess cavities and tuberculous foci

release an array of bacterial products, including noxious endotoxins which destory the endothelium. Local tissue hypoxia victimises the endothelium, which when damaged plays a major role in the initiation of intimal and medial vascular changes. The insulted endothelium triggers the migration of modified smooth muscle cells into the media, and stimulates dormant vasoformative reserve cells. Chronic diseases of the lung create a hypoxic environment in a variety of ways (Figure 4).

Jansen *et al*[5] in an account of conditions which predisposes to bacterial infection in chronic obstructive lung disease highlights the role of inflammatory mediators and bacterial endotoxins in inducing vascular damage. Alterations in the blood vessels comprising of vessel remodelling, proliferation and enlargement with changes in the vessel phenotype have been demonstrated in mice in whom chronic airway inflammation was experimentally induced.

The importance of these morphological changes is of more than mere academic interest. The crucial role of pulmonary endothelium in regulating vascular tone and cell growth of the vessel wall has been stressed[6]. Dysregulation of pulmonary vasotone leads to perfusion impairment.

Medial hypertrophy and intimal proliferation contribute to impaired perfusion. Barbera *et al*[7] in their study of pulmonary vascular abnorma-

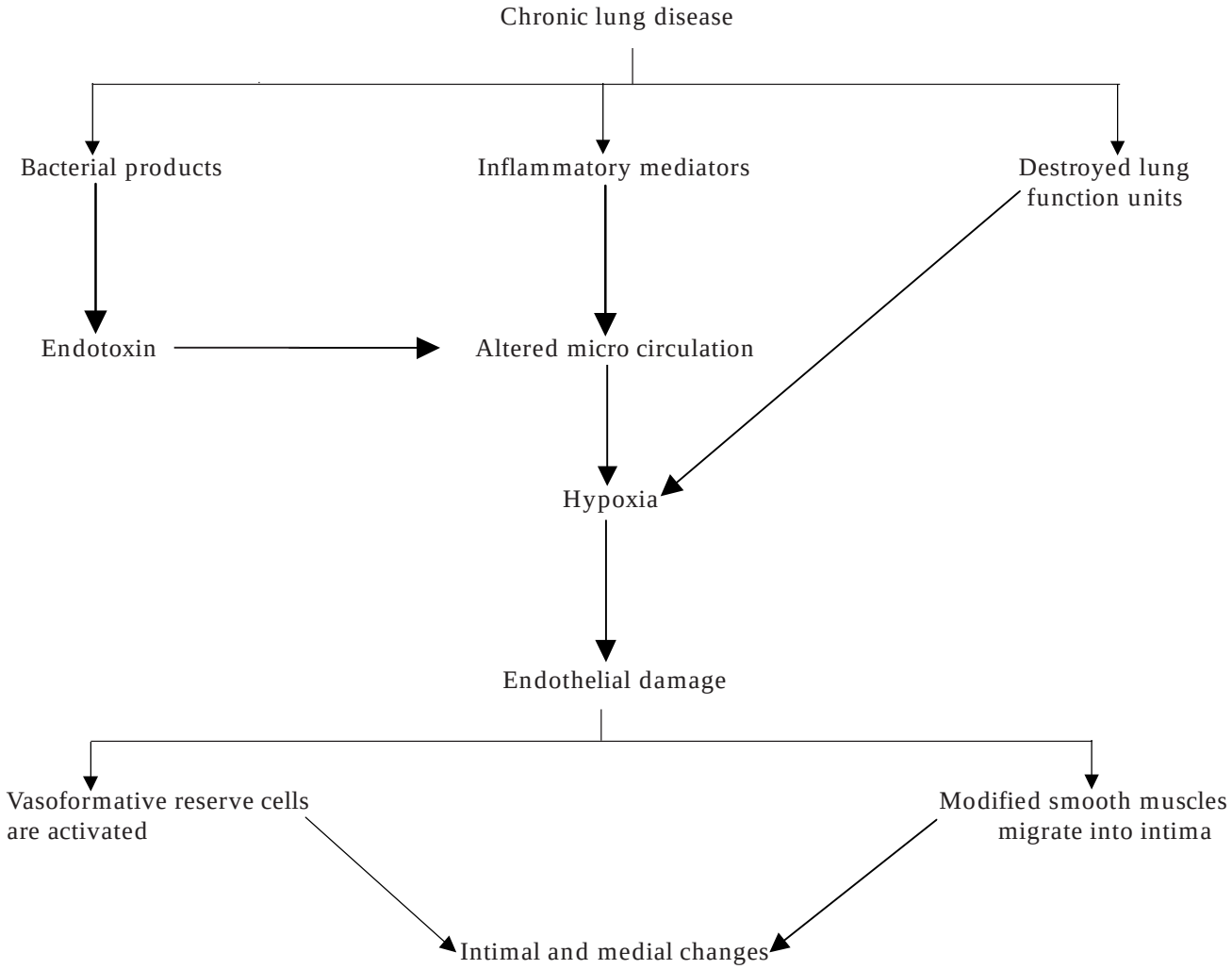

Figure 4. Impact of lung disease on vascular morphology.

lities and ventilation perfusion relationships in patients with mild chronic obstructive pulmonary disease documented a pronounced intimal enlargement in the group of patients with airflow obstruction and lowered response to oxygen.

Increased arterial resistance which is encountered in post-obstructive pulmonary vasculopathy (POPV) as experimentally demonstrated by Michel and Hakim[8] was attributed to increased percentage medial muscle thickness, peripheral muscularisation and focal intimal thickness. An increase in medial thickness also partially explains the hyperreactivity of arteries to serotonin and veins to histamine.

The impact of changes brought about by morphological abnormalities of blood vessels is borne by the already injured tissue, permitting a progression into irreparable damage.

However, recognition of these vascular changes does not always imply concomitant hypertension. None of the cases in this study had associated hypertension and in the previously mentioned study by Cyr *et al*[4] pulmonary arterial medial hypertrophy and intimal fibrosis were described in resected lung tissue from patients with idiopathic spontaneous pneumothorax, none of whom had hypertensive pulmonary vascular disease. The point to be highlighted is that in a setting of chronic inflammation and fibrosis in the adjacent lung, surgical pathologists should cautiously interpret the significance of medial hypertrophy and intimal fibrosis of muscular pulmonary arteries.

The value of understanding the spectrum of morphological changes would be greatly enhanced if effective therapeutic strategies could be designed to modulate hypoxia, reverse the inflammatory process and stabilise the fibroblastic process. Studies have successfully evaluated the role of laser biostimulation in the therapy of destructive lung disease[9] and experiments on mice to document reversal of microvascular remodelling by dexamethasone therapy has shown promising results[10].

In conclusion, this study highlights the salient morphological changes of pulmonary vasculature in destructive lung disease, while simultaneously stressing the need to avoid over interpretation of vascular changes of lung disease as implying hypertensive pulmonary disease.

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REVIEW ARTICLE

Premenstrual Asthma

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ABSTRACT

Gender differences have been recognized in asthma. Specifically in women, an exacerbation in symptoms occurring a few days prior to the onset of menstruation constitutes a phenotype that is not yet fully understood. This phenomenon, called "premenstrual asthma," has been reported to affect upto 40% women with asthma. This article reviews the literature on prevalence, effect of menstrual cycle on symptoms and lung function and discusses the proposed mechanisms of pathogenesis including the effects of female sex hormones on symptoms and β_2 adrenergic receptor function, and the role of airway inflammation. Finally, the various treatment options are presented.

Key words: *Premenstrual asthma, Women, Asthma.*

[Indian J Chest Dis Allied Sci 2005; 47: 109-116]

INTRODUCTION

There is some evidence to suggest that women are more frequently and severely affected by asthma. From 1982 to 1992, the prevalence of asthma among women increased by 82% (from 2.9% to 5.4%) compared with an increase of 29% among men (from 4.0% to 5.1%) in the USA[1]. During these same years, asthma mortality increased among women by 59% *versus* a 34% increase among men. Seventy-five per cent of adult patients admitted to hospitals for asthma are women. In a study in 67 hospitals in five counties of southeastern Pennsylvania, USA, patients admitted for asthma treatment (33, 269)[2] were reviewed. It was also observed that female asthmatic patients experienced longer hospital stays per admission as well. These data indicated that adult females were more severely affected by asthma and raised the possibility that hormonal or biochemical differences related to sex may play a role in the pathophysiology of asthma[2].

Gender differences in severity may have their origin in differences in the pathogenetic mechanisms, variations in pathophysiology and differences in response to treatment. On the other hand, the differences may not be biological in origin but may be related to social, economic, environmental and cultural factors that would vary from region to region. The available information is too scanty to allow any meaningful hypothesis to be developed regarding the reasons underlying gender differences in asthma.

While the well- known triggering factors for asthma such as allergens, viral respiratory infections, certain drugs, exercise and environmental irritants are equally relevant for

[Received: January 29, 2004; accepted: April 23, 2004]

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both male and female asthma patients, the latter have to contend with another factor - the effect of female sex hormones on asthma. Though there is evidence that these definitely play a role, the precise actions of the sex hormones and the mechanisms involved remain to be defined. Many of the studies carried out so far have been inconclusive and even contradictory. From menarche to menopause, these hormones exert a cyclical effect on the control of asthma.

It has been recognised that many women have the nadir of their control just a few days before the menstrual periods. This presentation of asthma in females has been described as "premenstrual asthma". However, as some patients with cyclic variation in symptoms may have exacerbation at other times during a menstrual cycle, other terms that have been used to describe this phenomenon include "menstrual-linked asthma", "menstrual-associated asthma", and ''perimenstrual asthma". For the sake of uniformity, the term "premenstrual astham (PMA)" will be used in this review.

Patients with PMA present with worsening of asthmatic symptoms and pulmonary functions in the late luteal phase of the menstrual cycle. Accurate diagnosis is dependent on a detailed history and the demonstration of premenstrual dip in peak expiratory flow or other measures of airway function. Up to 40% of female asthmatic subjects report a premenstrual deterioration in their condition[3-7]. Periodic variation in symptoms and airways function, and β_2 adrenergic receptor responsiveness have been documented in several studies over the last two decades although other studies have failed to confirm these. The pathogenic and therapeutic role of sex hormones in patients with PMA remains unclear[8-10].

Prevalence

The exact prevalence of this phenomenon is unclear as studies have involved small numbers in hospital clinics. Large-scale community-based studies are required to estimate its true prevalence. Questionnaires and twice daily peak expiratory flow measurements have been used to evaluate the effects of the menstrual cycle in asthmatic women. Thirty-six subjects out of 102 stated that their asthma worsened just prior to or at the time of their menses[3]. Daily monitoring of peak expiratory flow rate (PEFR) showed a significant reduction at the time of menstruation in those who worsened compared with those subjects who were unaffected. Cycle length was signficantly shorter in the group who worsened but the duration of the menses was not significantly different.

Of 57 women with asthma, 19(33%) had significant worsening of total pulmonary symptom scores during either the premenstrual period, the menstrual period, or both with maximum increase in dyspneoa, wheezing, and chest tightness during the premenstrual period[4]. Logistic regression analysis comparing women with and without worsening of their asthma around menstruation revealed that the former group reported significantly more severe wheezing in general and also more severe pulmonary symptoms during the premenstrual period. Of the women whose asthma was affected by menses, 13(68%) had been hospitalized for asthma but only 10(26%) of the women who were unaffected. Both dysmenorrhea scores and premenstrual symptom scores correlated significantly with baseline pulmonary symptom scores in the premenstrual asthma group. Indeed, a premenstrual fall in PEFR has been demonstrated even in those who have previously not been aware of this phenomenon[6].

Cyclical variation in symptoms

Forty per cent of women reported premenstrual deterioration in their symptoms and this was confirmed by peak flow recordings[5]. No correlations were found between premenstrual exacerbation of asthma and symptoms of premenstrual tension, consumption of aspirin, use of the contraceptive pill, cycle length, or behaviour of asthma during pregnancy. Other studies have similarly recorded cyclical variations in asthma symptoms[3,4,6,7]. A major limitation of many of these studies has been the usually small sample size. In a 9-week study consisting of two complete menstrual cycles, to

characterize and compare asthma symptoms with premenstrual symptoms (mood, physical), 10 out of 14 subjects had significant relationships between the two, whereas six had significant relationships between PEFR and premenstrual symptoms[11].

The relationship between asthma symptoms and the phase of the menstrual cycle is not clear. Some studies have even reported a lack of definite changes in asthma severity over the different phases of the menstrual cycle. Zimmerman *et al*[12] studied a large sample of 288 women and observed that only 13% of the subjects reported reproductive factors, including menses, as a personal asthma trigger. Further, the occurrence of symptoms had no cyclical variation.

It would be logical to assume that PMA should be associated with a greater frequency of acute exacerbations leading to emergency room visits. However, this is controversial. Zimmerman *et al*[12] observed that emergency department (ED) visits for asthma exacerbations in women were more frequent during the preovulatory menstrual phase (days 5 to 11) than in the perimenstrual phase (days 26 to 4). In addition, the phase of the menstrual cycle on presentation to the ED had no relationship to acute or chronic asthma severity. This contradicted another study, which noted an increase frequency of ED asthma visits by women during the perimenstrual phase[13]. However, in the former study[12] few women reported that reproductive factors, such as menses, were important triggers for their asthma exacerbation. Another reason for the differences in the studies may be related to access to health care as well as factors causing delays in seeking medical attention and to the rate of worsening of clinical control.

Effect of menstrual cycle on bronchial hyperresponsiveness and skin reactivity

Most studies have not shown any changes in airway responsiveness during the menstrual cycle. These have used methacholine[6,14] and histamine[15] which are agents that act directly on airway smooth muscle. Increased responsiveness to adenosine monophosphate (AMP) has however been reported. AMP induces bronchoconstriction indirectly by activating mast cells to release bronchoconstrictor mediators[16]. It has been suggested that increased AMP responsiveness during the luteal period is caused by sensitisation of adenosine receptors on mast cells by sex hormones resulting in a lower threshold for mediator release in response to adenosine.

The influence of female sex hormones may be there on skin prick test reactions to histamine and allergen with greater weal and flare reactions having been reported during the early luteal phase[17].

Menstruation and airway function

Objective evaluations of airway function during the menstrual cycle in women with stable asthma have yielded inconsistent results. Some studies have noted worsening symptoms and / or decreases in PEFR in the premenstrual and menstrual period, whereas others found no changes in symptoms or spirometric parameters[3,5,6,8,14,15,18]. Airway function was not related to hormone levels[6].

One report found a marked decrease in PEFR coinciding with ovulation[19]. Other studies found a discordance between symptoms and spirometric measurements during the menstrual cycle[6,14]. The decrease in lung function has also been reported to be small in the perimenstrual period in patients with stable asthma in one study so that it may not translate into exacerbations of sufficient severity to require ED care.

Variation in lung function over the menstrual cycle has also been studied in healthy women. Pauli *et al*[6] reported that normal volunteers showed no significant changes in symptoms, peak flow rates, spirometric parameters, or airway reactivity over the menstrual cycle. Intrasubject and diurnal variability in PEFR was minimal in non-asthmatic women; similarly, intersubject variability was relatively low. The menstrual cycle appeared to have little effect on PEFR in healthy non-asthmatic Asian women[20].

Proposed mechanisms for PMA

Role of female sex hormones

The effects of the menstrual cycle on the expression of asthma have been attributed to changes in progesterone and / or estradiol levels that affect airway function or inflammatory processes. This has, however, not been proved. Current evidence does not allow identification of the responsible hormone or hormones, or whether absolute levels or changes in hormone levels are most important. In one study[6], changes in symptoms were not related to the absolute levels of circulating progesterone and estradiol.

A role for female sex hormones has been postulated though the mechanism of their action remains to be elucidated[8]. Furthermore, it has recently been reported that hormone replacement therapy may increase the risk of developing asthma in postmenopausal women and this may be related to the dose of the oestrogen component and duration of use[10].

Both exogenous progesterone and estradiol administration have been reported to improve asthma in women[8,9,19,21]. In a few patients, intramuscular supplementary progesterone eliminated the premenstrual fall in PEFR and allowed better control of asthma with lower doses of systemic steroids[9]. Estradiol administration has been demonstrated to decrease symptoms, cyclic variability in PEFR, and airway reactivity in premenopausal asthmatic women[8,22]. However, estrogen replacement therapy is associated with a greater risk of developing asthma in postmenopausal non-asthmatic women and worsening of disease activity in postmenopausal asthmatics[10,23]. Zimmerman *et al*[12] suggested that hormonal factors have little influence on the severity of asthma or response to therapy once an exacerbation has begun. Studies have found no association between menstrual phase on ED presentation and acute asthma severity, as measured by PEFR or admission status[12,13]. Another study found no correlation of estradiol concentrations with the severity of bronchospasm or need for hospitalization[24].

PMA and a beneficial response to estradiol may be more likely in women with severe asthma. The administration of estradiol during the late luteal phase of the menstrual cycle to a woman with severe asthma with PMA was associated with improved asthma symptoms, pulmonary function, PEFR, and lower serum eosinophil protein X and urinary leukotriene E_4(LTE_4) biomarker concentrations[25]. This evidence is the form of a case report only. On the other hand, exogenously administered estradiol did not have a significant effect in women with premenstrual asthma whose asthma was classified predominantly as mild and under excellent control[26]. Again, this conclusion was based on a study on only 12 patients.

In another case report of a woman with premenstrual asthma, daily peak flow readings and every other day hormonal studies of progesterone and estrogen both demonstrated a positive correlation between the serum progesterone and the peak flow readings. The addition of intramuscular progesterone (75 mg daily) to the bronchodilators eliminated the premenstrual dips in peak flow, and daily doses of prednisolone were reduced to 5-10 mg. This suggested that a rapid fall in serum progesterone may play an important role in the pathogenesis of premenstrual asthma[27].

A recent review of literature on the effect of estrogen and progesterone on asthma describes the positive effects of these hormones on lung function across the life span of women[28]. Oral contraceptives and hormone replacement therapy are associated with improved pulmonary function and decrease in asthma exacerbations. This has, however, not been consistently observed and there is no definite evidence whether use of oral contraceptives abolishes PMA. The strength of evidence is however weak as most of the studies that have been carried out are based on small sample sizes and even include single subjects.

Role of beta-adrenergic receptor responses

Female sex steroid hormones have a regulatory role on β_2 adrenoceptor function and it has been postulated that abnormal β_2 adreno-

ceptor regulation may be a possible mechanism for premenstrual asthma. It has been shown that cyclical changes in lymphocyte β_2 adrenoceptor function occur during the menstrual cycle in normal women with greater β_2 adrenoceptor density and isoprenaline responsiveness in the luteal phase during the premenstrual period[29]. Further support for this role is provided by *in vitro* studies which show that female sex steroid hormones potentiate the bronchorelaxant effect of catecholamines[30]. Further, it has been shown that administration of exogenous progesterone, but not estrogen, in healthy women during the follicular phase produced upregulation of lymphocyte β_2 adrenoceptor density[31].

In a study investigate the influence of the menstrual cycle on airway responsiveness and β_2 adrenoceptor function in 15 stable female asthmatic patients without subjective complaints of PMA, there was no change in lymphocyte β_2 adrenoceptor parameters or in airway β_2 adrenoceptor responses to salbutamol between the two follicular and luteal phases although there was an appropriate rise in female sex hormones during the luteal period[16]. This suggested that β_2 adrenoceptor regulation in female asthmatic subjects shows a loss of the normal cyclical pattern. Further, in contrast to the finding mentioned above, it has been shown that administration of exogenous progesterone, but not estrogen during the follicular phase produced a decrease in lymphocyte β_2-adrenoceptor density and cAMP response in asthmatic women[32]. However, oral contraceptive pills, with varying estrogen and progesterone contents were not found to affect β_2-adrenoceptor regulation and function in stable female patients without a history of premenstrual asthma[33].

Role of inflammation

Asthma an inflammatory airways disease. Cyclic fluctuations in the degree of airway inflammation may underlie the precipitation of symptoms in female patients. This has been explored only recently in a small study in 11 women who complained of PMA[34]. Significant changes were in expired air nitric oxide levels, day-time symptom scores, and eosinophils in induced sputum before and after menstruation. Another study in five women investigated the role of cellular mediators released from inflammatory cells in the airflow limitation during PMA[35]. Serum levels of leukotriene C_4 (LTC_4) were significantly higher during episodes of PMA. However, other cytokines and mediators including interleukin -1β (IL-1β) interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), granulocyte macrophage-colony stimulating factor (GM-CSF), histamine, leukotriene B_4 (LTB_4) and platelet-activating factor did not change. Patients without PMA did not show any significant changes in LTC_4. Whether such a phenomenon occurs consistently has not been investigated in detail. There is also no explanation for cyclical changes in the degree of airway inflammation and whether hormonal fluctuations are responsible.

Psychological factors

The relation between menstrual cycle timing, panic attacks, and diagnosis of asthma was explored in one study[36]. No significant differences were identified for psychological or psychophysiological measures with menstrual cycle phase as a factor. It appears unlikely that PMA is a psychological problem.

Role of non-steroidal antiinflammatory drugs

Non-steroidal antiinflammatory drugs such as aspirin are well known triggering factors in many patients with asthma. Whether PMA was linked to intake of aspirin or related drugs was investigated by Forbes *et al*[37]. The hypothesis was rejected.

Treatment

Clinical experience has shown that intensification of treatment recommended by current asthma guidelines including inhaled corticosteroids is usually sufficient to control symptoms during episodes of PMA. However, none of the guidelines recommend any specific intervention including prophylactic increase in the dose of inhaled steroids or addition of a second drug such as a long acting β_2 agonist or theophylline. Other than standard anti-asthma therapy,

certain specific interventions have been investigated. Therapeutic use of estrogens and oral contraceptive pills has been discussed above.

Oral administration of pranlukast, a leukotriene receptor antagonist was shown to significantly counter decreases in PEFR and improve asthma symptom scores in five patients with PMA[35]. About 20% of the women with asthma, under chronic inhaled steroid treatment had premenstrual exacerbations of asthma. In 54% of them, it could be prevented by the use of long-acting bronchodilator, salmeterol, during the 10 days leading up to the menses, and partially prevented in another 15%. In the remaining 31%, this intervention was not effective[38].

Gonadotrophin-releasing hormone-analogue therapy to suppress gonadotrophin secretion and ovarian function has been proposed as a rational and innovative adjuvant treatment for PMA in cases of severe premenstrual asthma[39]. This treatment resulted in improvement in respiratory symptoms, the absence of PEFR dips premenstrually, a reduction in maintenance prednisolone dosage and no further hospital admissions during a follow-up period of 14 months.

Quality of life in PMA

Asthma is a disease that can result in varying degrees of restriction in the physical, emotional and social spheres of a patient's life. Effectiveness of asthma treatment has traditionally been assessed by measuring the change in clinical outcome parameters such as expiratory flow rates, symptoms and the need for other medications. It has been assumed that if one or more of these indices has improved, then the patient's health-related quality of life must have improved. This may not be actually the case. Conversely, a patient may feel and function better, but this may not be captured by one of the conventional clinical outcomes. Assessment of disease-specific quality of life has gained widespread acceptance in the last decade because of an increased awareness of its importance as an independent outcome measure. This has been further facilitated by the development of instruments for developing disease-specific quality of life questionnaires with strong measurement properties[40]. Changes in quality of life have not been studied so far in subjects complaining of PMA.

Issues for future research in PMA

Given the increasing prevalence of asthma all over the world and the fact that nearly 40% of women may suffer from PMA, this phenomenon needs to be considered as a major management problem in asthma. Therefore, a better understanding of various aspects of PMA is required. As reviewed above, there are many issues in of PMA that are not well understood. In addition, there are several contradictions in literature.

The prevalence has been estimated from small samples in hospital or institution-based studies. Prevalence in the community is not known. Besides differences in the prevalence, the relationship between asthma symptoms and the phase of the menstrual cycle is not clear. Clinical factors associated with PMA are not clearly defined. Whether there are subsets of patients who may be more prone to develop PMA are not clearly defined. It is not known whether the phenomenon is reproducible, *i.e.* those who complain of this, do they do so in every cycle and those who do not, do they never get it? Epidemiological and clinical studies are needed to resolve these issues.

Objective evaluations of airway function during the menstrual cycle in women with stable asthma have yielded inconsistent results. Lung function evaluation has been usually done using home monitoring of PEFR. There has been no study on the changes in static lung volumes and bronchodilator responsiveness in patients who have a history of PMA. Alterations in the pathophysiology during PMA need to be studied further.

Cyclic fluctuations in the degree of airway inflammation have has not been investigated in any large-scale study. The relationship between changes in airway inflammation, measured non-invasively or by invasive means, and physiological changes in lung function has not been studied. Whether female sex hormones

modulate airway inflammation is not known. It has also not been investigated whether there is a cyclical effect on immune regulation. The current understanding of pathogenesis of PMA is inadequate.

The consequences of PMA on the daily living of patients need to be studied. These include social and economic consequences as well as the impact on general and asthma specific quality of life.

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CASE REPORT

Endobronchial Non-Hodgkin's Lymphoma

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ABSTRACT

A 23-year-old male presented with clinical and radiological features of left lung collapse. Fibre-optic bronchoscopy revealed a smooth globular mass almost completely occluding the left main bronchus. Needle aspiration and endobronchial biopsy from the mass revealed it to be a case of anaplastic large cell lymphoma, a subtype of non-Hodgkin's lymphoma. This report documents the rare presentation of non-Hodgkin's lymphoma as an endobronchial mass.

Key words: *Endobronchial lymphoma, Endobronchial mass.*

[Indian J Chest Dis Allied Sci 2005; 47: 117-120]

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) involves intrathoracic structures in about 43% of cases at some stage in the course of disease[1]. Mediastinal or hilar lymph node enlargement is the most frequent intrathoracic manifestation in patients with lymphoma, seen in 36% of cases in a large series[2]. The involvement of major airways is mostly due to extension from enlarged broncho-pulmonary lymph nodes[3]. The presentation of NHL as an endobronchial mass is extremely rare even in the presence of advanced disease.

CASE REPORT

A 23-year-old male, non-smoker was symptomatic for the last two months with chief complaints of cough with scanty mucoid expectoration, fever, progressively increasing breathlessness, loss of appetite and weight loss of about 8 kg. There was no history of haemoptysis, chest pain or wheezing. On evaluation at a peripheral hospital, the patient was found to have normal chest radiograph and was treated symptomatically. His symptoms, however, persisted and a repeat chest radiograph after one month showed a homogenous opacity in the left upper and middle zones along with volume loss. The patient was started on antituberculosis treatment on the presumptive diagnosis of pulmonary tuberculosis and was referred to our centre for further management.

At admission, the patient was febrile, had heart rate 126/min and a respiratory rate 30/min. There was no pallor, clubbing, lymphadenopathy or pedal oedema. Chest examination revealed findings consistent with collapse of left lung. The rest of systemic examination was unremarkable. On investigation, haemoglobin, blood counts and metabolic parameters were within normal limits. He was human immunodeficiency virus (HIV) seropositive by the enzyme linked immunosorbent assay (ELISA) method. Sputum smear examination by Gram's

[Received: March, 18, 2004; accepted after revision: July 27, 2004]

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and Ziehl-Neelsen's stains were negative. Chest radiograph showed homogenous opacity in the left upper and mid zones along with features suggestive of collapse of the left lung (Figure 1). A high resolution computed tomography of the chest revealed a 4.6×3.7 cm soft tissue mass at the left main bronchus extending to involve the left upper lobe, with mediastinal displacement to left (Figure 2).

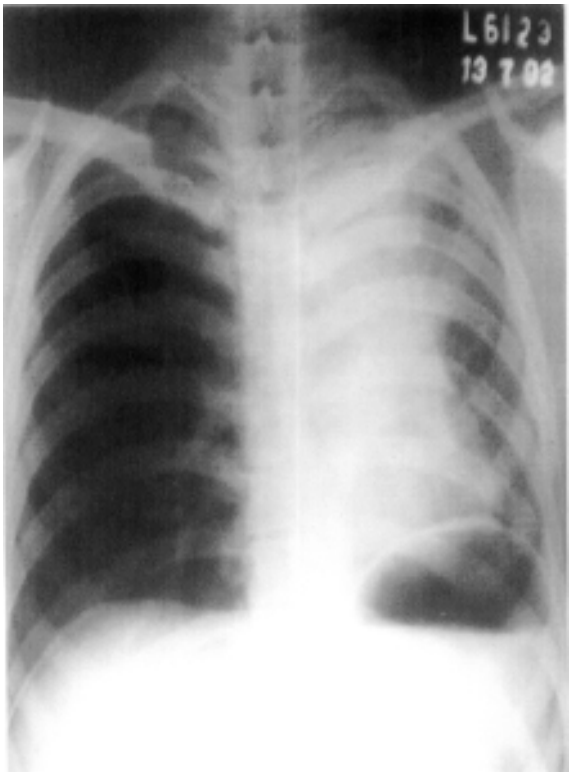

Figure 1. Chest radiograph (postero-anterior view) showing homogenous opacity in the left upper and mid zones with features of volume loss.

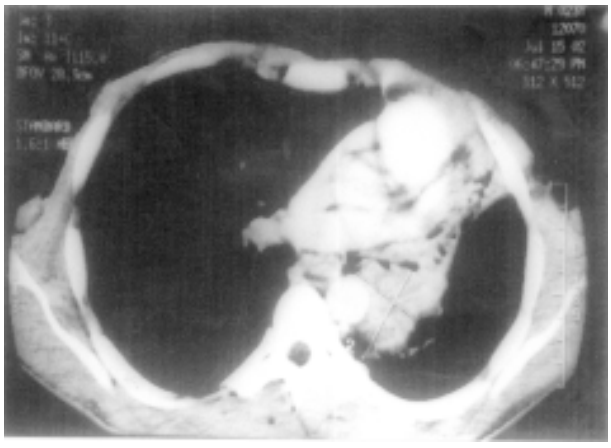

Figure 2. Computed tomographic scan of the chest showing 4.6×3.7 cm soft tissue mass compressing the left main bronchus and mediastinal shift to left.

Fibreoptic bronchoscopy revealed a globular smooth mass causing near complete obstruction of the left main bronchus (Figure 3). Endobronchial needle aspiration and biopsy of the mass was done. The needle aspiration showed large cells with moderate cytoplasm and convoluted nuclei with hyperchromatism and nucleoli.

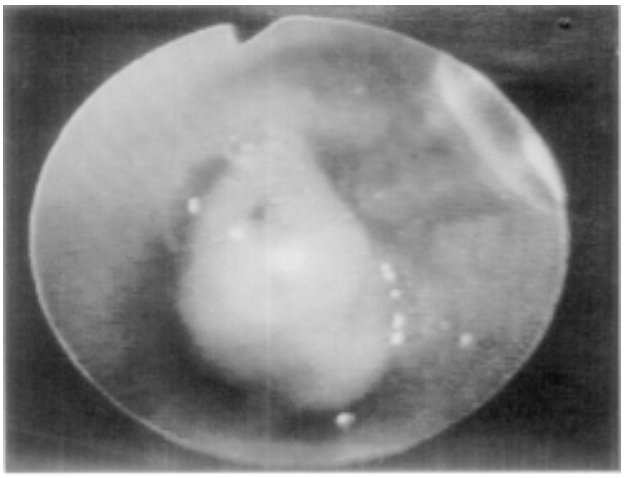

Figure 3. Bronchoscopic view of left main bronchus showing globular smooth mass.

Histopathological examination of the endobronchial biopsy showed overlying ciliated pseudostratified columnar epithelium, large closely packed cells with scant cytoplasm and pleomorphic hyperchromatic nuclei with mitotic figures in the vascular lumen and perivascular areas (Figure 4). Immunohistochemical staining was positive for Ki -1 (CD30) antigen and anaplastic lymphoma kinase (alk) protein which is diagnostic for anaplastic large cell lymphoma. While in the hospital, the patient developed a mass on the medial aspect of the right thigh and left supraclavicular region and skin nodules in the left axillary region. Fine needle aspiration cytology (FNAC) of the soft tissue swelling and skin nodules over the left thigh showed features similar to aspiration cytology of endobronchial mass. Bone marrow aspirate showed diffuse infiltration by lymphoma.

The patient was managed with chemotherapy in the form of dexamethasone, cyclophosphamide, doxorubicin, vincristine, and etoposide. The patient initially showed good

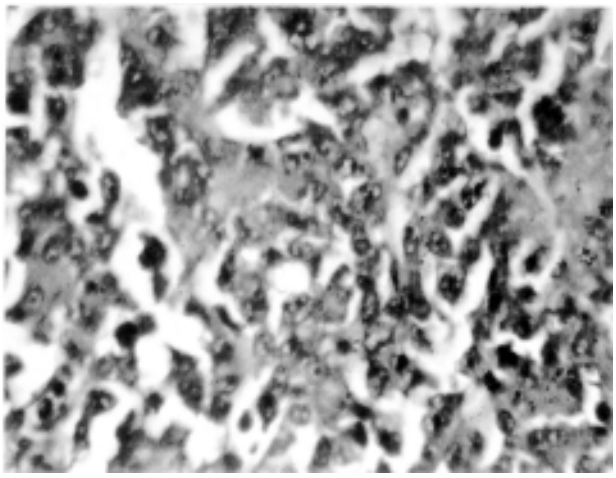

Figure 4. Photomicrograph of endobronchial biopsy showing closely packed cells with scant cytoplasm and pleomorphic hyperchromatic nuclei with mitotic figures in the vascular lumen and perivascular areas (H&E, × 600).

improvement with chemotherapy with dramatic regression of the skin nodules and resolution of the collapse of the left lung. But after four cycles of chemotherapy the patient's condition detoriorated with recurrence of the mass which now occupied almost the entire left hemithorax and appearance of fresh skin nodules over the trunk. The patient died within five months of the diagnosis.

DISCUSSION

The first case of endobronchial NHL was described in 1955 by Dawe *et al*[4]. Since then, about 50 cases have been described in the literature[5-9]. In an autopsy study of patients with NHL (n=55), where none of the cases showed endobronchial involvement[10]. In another autopsy study, only one patient had endobronchial lesion out of 93 patients with pulmonary lymphoma[11]. These observations suggest that endobronchial involvement is very rare in patients with NHL.

The involvement of tracheobronchial tree is more common in Hodgkin's lymphoma than in NHL. The most common involvement is displacement or narrowing of airway lumen by enlarged mediastinal or hilar lymph nodes[3], followed by diffuse peribronchial infiltrates resembling lymphangitis carcinomatosis[12] and as an endobronchial mass like in the present case. The endobronchial lesion can be solitary [1,3] or multiple[5-7]. The symptoms depend upon the type of involvement of intrathoracic sites and the morphological subtype of NHL. The anaplastic large cell lymphoma accounts for about 2% of all NHLs[13]. The most common extanodal site of occurrence of this type of lymphoma is the skin and its primary occurrence at other extranodal sites is rare[9]. The endobronchial involvement by anaplastic large cell lymphoma is extremely rare and apart from the present case the authors could retrieve only one other case report in a 16-year-old girl with similar presentation[9]. The anaplastic large cell lymphoma usually occurs in young males and more than 50% patients present in stage III/IV and have systemic symptoms[13] like in the present case. Chest radiograph shows the features of atelectasis or obstructive pneumonitis in most of the cases with endobronchial involvement[3].

There are different mechanisms postulated for the development of endobronchial lesions in lymphoma. These include direct invasion from adjacent mediastinal or parenchymal disease, lymphatic spread to peribronchial connective tissues or hematogenous spread[9]. In the present case, the endobronchial involvement was possibly due to extension from the lung mass. Bronchoscopy and endobronchial biopsy is the definitive investigation. Treatment depends on the extent of involvement of the tumour and the general condition of the patient. Most of the patients are managed with chemotherapy and/or radiotherapy. The five year survival rate for anaplastic large cell lymphoma is about 75%[13].

To conclude, NHL rarely presents as an endobronchial growth and only histopathology can differentiate it from other benign and malignant endobronchial masses.

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CASE REPORT

Asymptomatic Lymphangitis Carcinomatosis due to Squamous Cell Lung Carcinoma

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ABSTRACT

Lymphangitis carcinomatosa most commonly due to primary malignancy originating in the breast, stomach, pleura and prostate but may also originate from the lung itself. It is clinically characterised by progressing dyspnoea with or without cough even at an early stage. We report the case of a patient with squamous cell lung cancer presenting with asymptomatic lymphangitis carcinomatosa.

Key words*: Lymphangitis carcinomatosa, Squamous cell lung cancer, Transbronchial lung biopsy.*

[Indian J Chest Dis Allied Sci 2005; 47: 121-123]

INTRODUCTION

Secondary neoplastic diseases of the lung frequently present as lymphangitis carcinomatosa. It most commonly originates from primary malignancy in the breast, stomach, pleura and prostate[1,2] but may also originate from the lung itself. The most frequent cell types of lung cancer causing lymphangitis carcinomatosa in patients with lung cancer include small cell carcinoma and adenocarcinoma. Lymphangitis carcinomatosa secondary to squamous cell lung carcinoma is rare.

Lymphangitis carcinomatosa is clinically characterised by progressing dyspnoea with or without cough even at an early stage. The primary tumour is obvious in most patients but may be occult in others. In the later situation, the diagnosis may be difficult to make as the clinico-radiological picture is often confused with other interstitial lung disorders such as pulmonary congestion, interstitial pneumonitis, pulmonary fibrosis, bronchioloalveolar carcinoma and granulomas.

We report the case of a patient with squamous cell lung carcinoma presenting with asymptomatic lymphangitis carcinomatosis.

CASE REPORT

A 61-year-old male patient was referred for evaluation as he was found to have abnormal chest radiograph during a routine health check up. He denied history of respiratory or constitutional symptoms except for vague pain chest. There was no history of any drug intake or exposure to any kind of pets, dust, fumes or smoke. There was no history of any respiratory or any other illness in the past as well.

On examination, he was of moderate built and nourishment. He had mild clubbing but did

[Received: January 9, 2004; accepted after revision: May 6, 2004]

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not have any pallor, cyanosis or pedal oedema. Neck veins were not engorged. Respiratory rate was 18/min. Physical examination of his chest revealed bilaterally symmetrical chest with normal vesicular breathing and no added sounds. Examination of cardiovascular, abdominal, neurological and musculo-skeletal systems did not reveal any abnormality. Review of his chest radiograph (Figure 1) showed bilateral coarse reticulo-nodular opacities of central distribution.

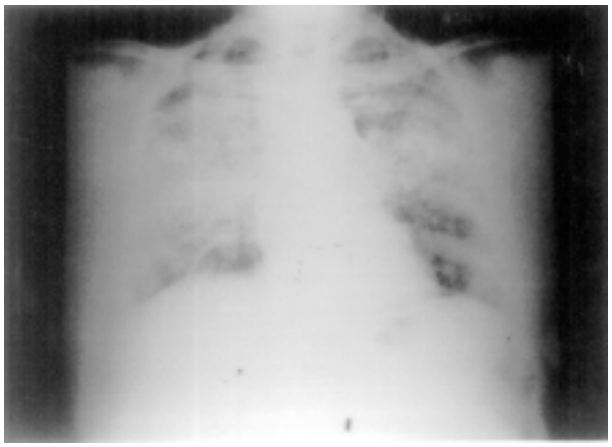

Figure 1. Chest radiograph (postero-anterior view) showing bilateral coarse reticulonodular opacities.

Laboratory examination revealed, haemoglobin was 12.4 g/dl, total leukocyte count 8,400/mm^3 with polymorphs 84%, lymphocytes 14%, eosinophils 1% and monocytes 1%. Blood sugar 90 mg/dl, and blood urea 18 mg/dl. Urine and stool examinations were normal. Mantoux skin test was negative. Spirometery showed moderate restrictive defect. Serum was negative for antinuclear antibodies. He was advised to undergo high resolution computed tomographic scan (HRCT scan) which he refused.

Fibreoptic bronchoscopy was essentially normal. Histopathology of the transbronchial lung biopsy (TBLB) revealed normal lung parenchyma infiltrated with sheets of moderately differentiated squamous cell carcinoma (Figure 2).

On the basis of this report, the patient was re-evaluated. Physical examination did not reveal any focal of systemic abnormality even at this

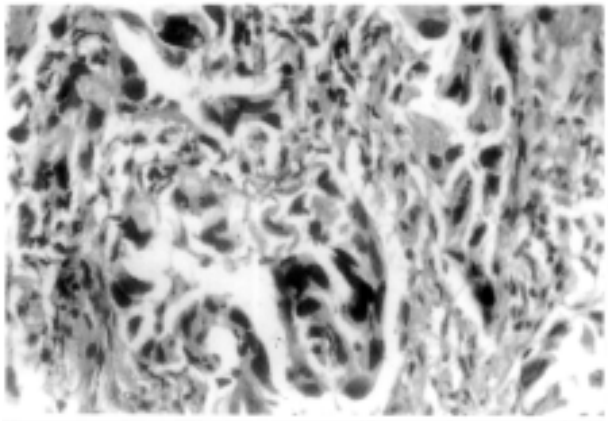

Figure 2. Photomicrograph of transbronchial lung biopsy showing sheets of squamous cell carcinoma (H & E × 40).

stage. Repeat chest radiograph was essentially similar to that shown in figure 1. Ultrasound examination of the abdomen did not reveal any organomegaly. Prostate specific antigen was 0.12 mg/μl. Computed tomographic scan (CT scan) of the thorax at this stage revealed bilateral interstitial septal thickening and nodular opacities in the lung parenchyma (Figure 3) along with enlarged mediastinal,

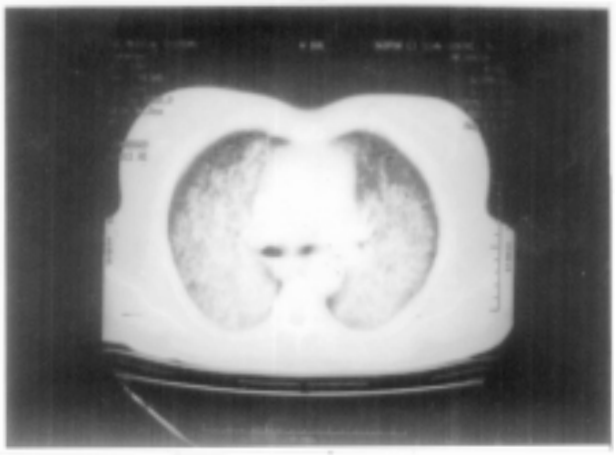

Figure 3. CT Scan of the thorax showing bilateral interstitial septal thickening and nodular opacities.

paratracheal, pretracheal and prevascular lymph nodes and a large well defined soft tissue dense mass lesion in the posterior segment of the right upper lobe (Figure 4). CT guided FNAC of the mass lesion revealed moderately differentiated squamous cell carcinoma. The patient refused for further management and was lost to follow-up.

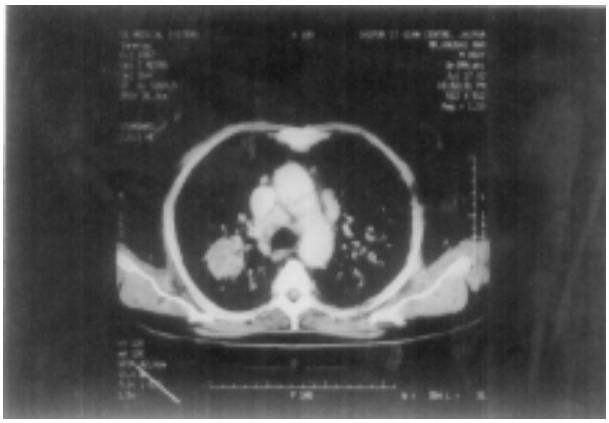

Figure 4. CT scan of the thorax cut showing a large well defined soft tissue dense mass lesion and enlarged pre-tracheal lymphnode.

DISCUSSION

This patient presented to us with bilateral interstitial lung lesions in his chest radiograph. He had no symptoms pertaining to primary lung carcinoma or the secondary neoplastic disorder of the lung. Basing on the initial clinico-radiological picture lymphangitis carcinomatosis was not considered in the differential diagnosis as a cause of interstitial pattern in the present patient. It was unexpectedly revealed at the histopathological examination of his TBLB specimen and was later shown to be secondary to squamous cell lung carcinoma of the lung itself with the help of the CT scan. The role of CT scan of the thorax in the evaluation of interstitial lung disorders has been amply emphasized by Grenier *et al*[3]. Unfortunately, our patient refused for CT thorax during the initial work up.

Lymphatic spared of neoplasm to lung may occur by two routes: *(i)* hematogenous dissemination followed by invasion of the interstitial lymphatics towards hilum or the periphery of the lung[1]; *(ii)* retrograde spread of the tumour within the lymphatic cannels[4] from the mediastinal and/or hilar and bronchopulmonary nodes to the periphery of the lung and pleura.

Involvement of mediastinal, paratracheal and pretracheal and prevascular lymph nodes in our patient suggests that lymphangitis carcinomatosa was probably due to retrograde spread. In hematogenous dissemination, bronchopulmonary and hilar lymph nodes are mostly free from the neoplastic disease. Lymphangitis carcinomatosis should always be considered in differential diagnosis of interstitial lung disorders.

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RADIOLOGY FORUM

It is proposed to extend the scope of the Radiology Forum of our Journal by inviting our readers as well as other workers in the field or Respiratory Medicine to submit brief report of patients with interesting clinical and radiological features for publication. These will be published, provided that :

(*a*) the condition is of sufficient clinical and radiological interest;

(*b*) photographs (10 cm × 8 cm) are of excellent quality for printing (Maximum : 3 photographs);

(*c*) the diagnosis in each case has been confirmed;

(*d*) the chest radiograph is accompanied by brief clinical account, not exceeding one page typescript.

All the material received for publication in the Radiology Forum will be evaluated to judge the suitability for publication by our experts panel.

Editor-in-Chief

CASE REPORT

Congenital Lung Hernia

Sushil Kumar Singh, Sanjay Pandey, Lalit Mohan Joshi and Shekhar Tandon

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ABSTRACT

We report a case of a congenital atraumatic lung hernia who underwent a successful operation.

Key words: *Lung hernia, Pulmonary hernia.*

[Indian J Chest Dis Allied Sci 2005; 47: 125-126]

INTRODUCTION

Lung hernia is a rare entity and is defined as the protrusion of the pulmonary tissue and pleural membranes through defects of the thoracic wall[1]. It can be congenital or acquired and may be cervical, thoracic or diaphragmatic in location. It is mostly acquired following trauma but can occur spontaneously after a bout of cough[2,3]. Although supraclavicular pulmonary herniation as a result of clavicle-sternal dislocation has been reported by Francois *et al*[1]. We report the rare occurrence of congenital atraumatic supraclavicular pulmonary herniation in a 9-year-old child.

CASE REPORT

A 9-year-old female child presented with a soft cystic mass in the right supraclavicular region since birth that has shown a recent increase in size. There was no history of trauma, any episode of cough, dyspnoea or pain. On examination the swelling located in the right supraclavicular region was (4 cm × 3 cm), non-pulsatile, cystic in consistency. Transillumination test was negative and needle aspiration revealed presence of air but no fluid. Chest radiograph revealed an area of hyperlucency in the right upper zone clearly protruding outside the thoracic cavity into the right cervical region without evidence of rib fracture or pneumothorax (Figure). Chest radiograph (lateral view)

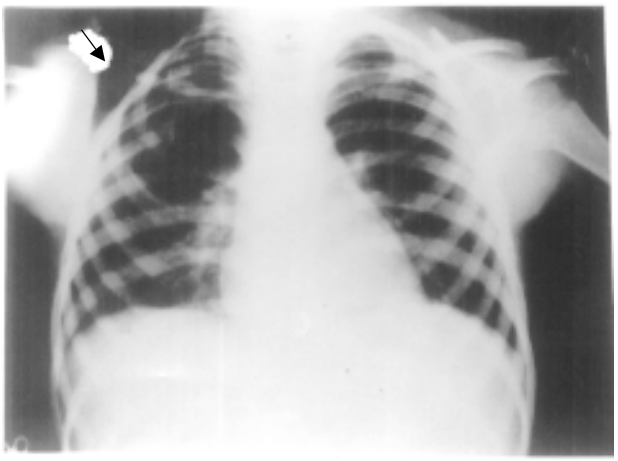

Figure. Chest radiograph (postero-anterior view) showing an area of hyperlucency in the right upper zone (arrow) extending and continuing into the right supraclavicular region.

[Received: February 16, 2004; accepted after revision: May 5, 2004]

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also showed the area of hyperlucency.

A right posterolateral thoracotomy was performed through the fifth intercostal space. The right upper lobe was found to be herniating into the cervical region. The part protruding was cystic and covered by a thick pleura. The cystic area of the right upper lobe was excised and the overlying thickened pleura plicated to reinforce the area of weakness. The patient did well and was discharged uneventfully and had no recurrence at one year of follow-up.

DISCUSSION

Less than 300 cases of lung hernia have been reported, of which 83% are acquired and 18% are congenital[2]. According to the location, 65% to 83% of all lung hernias are thoracic and the remaining 35% are cervical[4,5]. Only a few cases of diaphragmatic lung hernias have been reported thus far[2]. Most of the patients with lung hernias are asymptomatic. Symptomatic patients usually present with a soft reducible mass with or without pain. The precipitating factors may be trauma, a bout of cough, chronic obstructive pulmonary disease, inflammatory or neoplastic processes and chronic steroid use[3,5]. But in our case none of these precipitating factors were present.

Chest radiograph may or may not demonstrate the lung hernia but a computerised tomographic (CT) scan is diagnostic. In our case, the chest radiograph clearly showed the lung tissue herniating into the right cervical region. As this condition is rare and infrequent, Jacka *et al* and Reardon *et al*[6,7] did not perform CT scan as part of their evaluation.

Although intervention for herniation secondary to blunt injury is recommended, Francois *et al*[1] has suggested the possibility of conservative treatment in small asymptomatic hernias. Due to the recent increase in size and risk of incarceration of the lung tissue, we decided to operate on the patient with direct repair of the defect.

The present case highlights the rarity of the congenital, atraumatic, supraclavicular location of the lung hernia.

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CASE REPORT

Portopulmonary Hypertension in a Patient of Autoimmune Hepatitis

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ABSTRACT

A 35-year-old women presented with breathlessness and features suggestive of pulmonary hypertension. Further investigations revealed that she had autoimmune hepatitis and both portal and pulmonary hypertension. Pertinent literature is reviewed.

Key words: *Portopulmonary hypertension, Autoimmune hepatitis, Pulmonary hypertension, Liver diseases, Portal hypertension.*

[Indian J Chest Dis Allied Sci 2005; 47: 127-130]

INTRODUCTION

The wide spectrum of pulmonary vascular disorders in patients with liver disease and portal hypertension ranges from the hepatopulmonary syndrome (HPS) characterised by intrapulmonary vascular dilatations, to portopulmonary hypertension (PPHTN) in which pulmonary vascular resistance is elevated[1]. Initially described in 1951 by Mantz and Craige[2], PPHTN has been a rarely encountered syndrome of largely academic interest with uncertain clinical implications for patient management. Because of low prevalence, the clinical characteristics of PPHTN are largely unknown, and consequently, attempts to study this entity to develop screening strategies and implement potential therapies have been hampered[3]. There have been case reports[4-8] that have documented the development of pulmonary hypertension in patients with cirrhosis. Here we report PPHTN in a patient of autoimmune hepatitis.

CASE REPORT

A 35-year-old lady presented with progressively increasing breathlessness and fatigue for one year. She was admitted with swelling of both lower limbs and pain in right hypochondrium of 10 days duration. She denied having taken any medications to reduce her weight. Seven years back she had jaundice, and recovered within a month and was not investigated further at that time.

The patient was breathless at rest. She was icteric and pale, and had bilateral ankle oedema. Jugular venous pressure was raised. Breath rate was 30 per minute and other vital signs were normal. Cardiovascular and

[Received: December 3, 2003; accepted after revision: May 5, 2004]

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respiratory system examinations were essentially normal. Abdominal examination revealed palpable, soft and pulsatile liver two fingers below the right costal margin. Spleen was palpable three fingers below the left costal margin. Ascites was present.

Chest radiograph showed pulmonary artery prominence. Electrocardiogram (ECG) revealed evidence of right ventricular hypertrophy with right axis deviation. Laboratory studies showed microcytic hypochromic anaemia and total leukocyte count of 9400 cells/mm^3. Blood urea, serum creatinine and serum electrolytes were normal. Other investigations included total serum bilirubin 1.9 mg/dl, conjugated bilirubin 1.1 mg/dl, SGOT 1420 IU/L (normal 40), SGPT 980 IU/L (normal 40), and serum alkaline phosphatase 630 IU/L (normal 306). Blood immunoglobulin profile revealed raised immunoglobulin G (IgG) 3566 mg% (normal 1800) with normal levels of immunoglobulin A (IgA) and immunoglobulin M (IgM). All viral markers were negative. Serological tests for human immunodeficiency virus (HIV) were non-reactive. Rheumatoid factor, LE cell phenomenon and antinuclear antibody (ANA) were negative. Antismooth muscle antibodies were absent, however, anti-liver kidney mitochondrial (LKM) antibodies were positive with titer 1 : 30. Arterial blood gas analysis (ABG) showed pH 7.44, PaO_2 81 mmHg; and $PaCO_2$ 29 mmHg. Pulmonary function testing revealed mild restrictive pattern.

Doppler and ultrasound examination of the abdomen revealed coarse and heterogenous echotexture of liver. Portal vein was 11 mm at porta hepatis and superior mesenteric vein was 9 mm. Reversal of flow was shown in portal vein. Inferior vena cava and pelvic veins were normal and patent. Enlarged spleen with normal echotexture was evident with splenic vein being 6 mm at hilum. Liver biopsy (Figure 1) was suggestive of chronic active hepatitis.

Echocardiogram of patient revealed dilated right atrium, right ventricle and pulmonary artery. Right ventricular systolic pressure was 45 mmHg. Pulmonary artery systolic pressure was 68.5 mmHg. Global left ventricular (LV) ejection fraction was 60 percent. Contrast echocardiogram did not demonstrate right to left shunt.

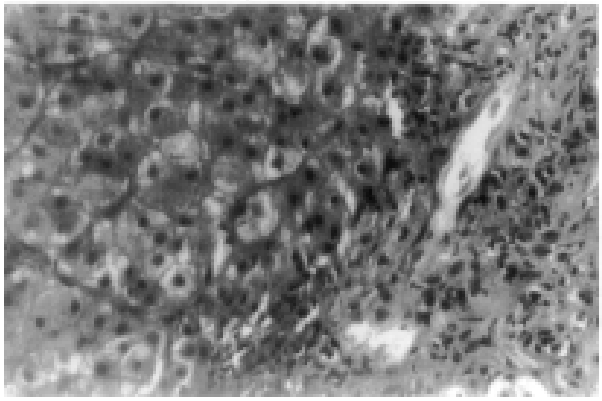

Figure 1. Photomicrograph showing mild chronic inflammatory infiltrate in portal tract with focal limiting plate destruction and portal fibrosis in the focal areas suggestive of chronic active hepatitis.

Magnetic resonance angiography for evaluation of pulmonary arterial system exhibited prominent main pulmonary artery measuring 3.3 cm; and right and left pulmonary artery measuring 1.4 cm and 2.2 cm respectively (Figure 2). There was no evidence of thrombus. Cardiac catheterisation showed mean pulmonary capillary wedge pressure (PCWP) 16 mm; mean pulmonary artery pressure was found to be 50 mmHg; mean right ventricular pressure was 43 mmHg; and right atrial pressure was 5 mmHg. Ventilation/perfusion scan of lungs did not suggest presence of thromboembolism.

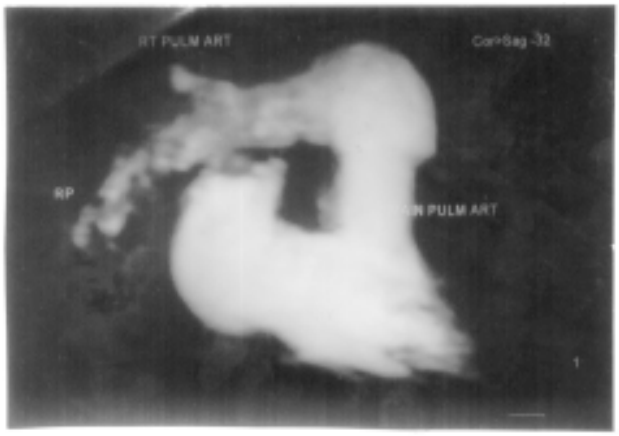

Figure 2. Magnetic resonance angiography for evaluation of pulmonary arterial system exhibited prominent main pulmonary artery measuring 3.3 cm. Right pulmonary artery is also visible measuring 1.4 cm.

Nifedepin 120 mg per day in divided doses and losartan 100 mg in a day was prescribed. She was symtomatically better.

DISCUSSION

Pulmoanry hypertension was initially considered unusual among patients of cirrhosis and portal hypertension[1]. Prevalence of clinical pulmonary hypertension in biopsy proven cases of cirrhosis has been found to be 0.61 percent[8].

The diagnosis of portal hypertension antedated that of PPHTN in majority of cases, but this case had presenting features suggestive of severe PPH. The diagnosis of portal hypertension was established later. Only 33% of cases of PPHTN were shown to have abnormal chest radiograph and 63% had ECG abnormalities[3]. In PPHTN, echocardiographic studies have shown that 63% cases have tricuspid regurgitation while 53% have dilated right atrium and 50% have been found with dilated right ventricle[3], all of these features were observed in the present patient. In setting of chronic liver disease, abnormal pulmonary functions, including presence of respiratory alkalosis has been well described[3,9]. The discussed case had respiratory alkalosis. Study by Kuo *et al*[3] has interestingly shown that $PaCO_2$ < 30 mmHg was essentially equivalent to the diagnostic ability of ECG and/or echocardiogram with a specificity of 0.90, sensitivity of 0.87, positive predictive value of 0.87 and a negative predictive value of 0.90.

Anti-nuclear antibodies are present in approximately 19% of cases of PPHTN[1] whereas other serological markers may be present in significant number of patients[9]. Only anti-LKM antibodies were detected in our patient in significant titers. Presence of anti-LKM antibodies along with raised serum immunoglobulins, deranged liver function tests, negative viral markers and characteristic histological picture of liver were suggestive of autoimmune etiology of chronic hepatitis in this patient.

A moderate increase in pulmonary artery pressure >30 mmHg is not unusual in patients with cirrhosis and portal hypertension[1]. This increase in pressure is generally passive due to increase in cardiac output and is associated with near normal pulmonary vascualr resistance and normal or increased PCWP. In contrast, a severe pulmonary hypertension with normal PCWP was rarely observed in cases with cirrhosis and portal hypertension[1]. Our case had severe pulmonary hypertension with normal PCWP. Three vascular abnormalities have been shown to be allies to cause the increase in pulmonary vascular resistance in PPHTN, *i.e.*, vasoconstriction, remodelling of muscular pulmonary artery walls and *in situ* microthrombosis[1].

To the best of our knowledge, any detailed report of a patient of portopulmonary hypertension with autoimmune hepatitis is not published. Only one retrospective study of 30 patients of PPHTN[1] mentioned autoimmune hepatitis as one of the causes of liver diseases to cause this entity with no further details.

The present case aims to draw the attention of the practicing cardio-respiratory physicians to keep in mind this uncommon cause of pulmonary hypertension which unless looked for, can be easily missed. Further, it also highlights the fact that it is not unusual for cases of liver disease with portal hypertension to present primarily with severe pulmonary hypertension.

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CASE REPORT

Acromesomelic Dysplasia with Bronchiectasis

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ABSTRACT

We report a rare case of acromesomelic dysplasia with bilateral bronchiectasis and obstructive sleep apnoea. Diagnosis of acromesomelic dysplasia was based on radiographs of whole skeleton.

Key words: *Acromesomelic dysplasia, Bronchiectasis.*

[Indian J Chest Dis Allied Sci 2005; 47: 131-134]

INTRODUCTION

Acromesomelic dysplasia is an extremely rare inherited progressive disorder, characterised by severe shortening of middle and distal segments of limbs but normal intelligence and facial appearance[1,2]. This occurs due to premature fusion of metaphyses of certain long bones[3]. Respiratory complications in the form of bronchiectasis, tracheomalacia, tracheal stenosis and obstructive sleep apnoea have been reported in various other skeletal dysplasias but not in the acromesomelic variety[1,4,5]. We report a case of acromesomelic dysplasia with bronchiectasis and obstructive sleep apnoea.

CASE REPORT

A 40-year-old female presented with symptoms of recurrent respiratory tract infection, dyspnoea on exertion and bony deformities since childhood. She had received blood transfusions during hysterectomy for menorrhagia eight years ago. On clinical examination there was grade III clubbing. She was 132 cm tall with upper segment (US) of 66 cm and lower segment (LS) of 66 cm and US to LS ratio of one. Body mass index (BMI) was 17.2 kg/m^2. There was frontal bossing with shortened (mesomelic) forearms, widened wrists, shortening of left fourth finger, shortening of right second and third fingers radial deviation of hands with limited extension of both elbow joints. She also had mild genu varum, mild varus deformity of foot, shortened first and fifth toe on both sides, fanning of second, third and fourth toe on left side and medial deviation of second, third and fourth toe on right side. There were bilateral coarse crepitations on auscultation of the chest. Cardiovascular system examination revealed a loud second heart sound in the pulmonary area. Abdominal, neurological and ophthalmologic examinations were unremarkable.

[Received: December 31, 2003; accepted after revision: April 16, 2004]

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On investigation, haemoglobin was 11 g/dl; total leukocyte count was 9500 mm^3 with neutrophils 62% and lymphocytes 38 percent. The total lymphocyte count was 3600 mm^3. Other biochemical parameters were within normal limits. Chest radiograph showed presence of cystic opacities bilaterally in both lung fields. Radiograph of both wrists (Figure 1) revealed generalised periarticular osteopenia,

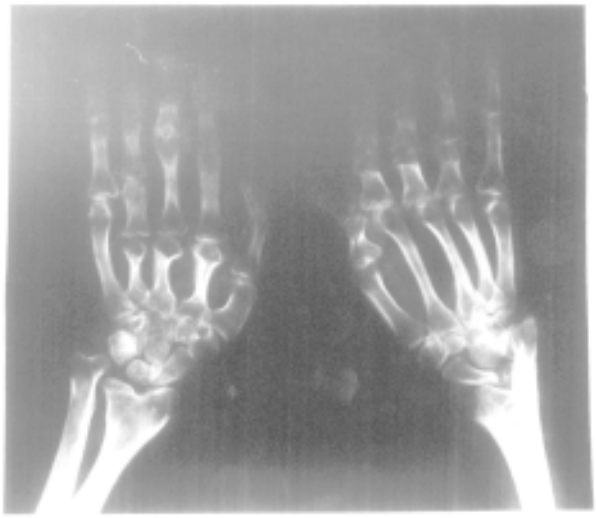

Figure 1. Radiograph of both wrists showing generalised periarticular osteopenia, short first, second and third metacarpal bone. Discrepant shortening of fourth proximal, mid and distal phalangial bones as compared to other phalangeal bones.

short first, second, third and fourth metacarpal bones. Discrepant shortening of fourth proximal mid, distal phalangial bones comapred to other phalangeal bones. Radiograph of elbows showed deformity and bowing of radii which was more on right side than on left side, also was more proximal than distal with a widened intraosseous space (Figure 2). Exuberant outgrowths were seen along medial and inferior surface of humerus. Radiograph of feet revealed bilateral congential varus deformity. Radiograph of both knee joints, both hip joints and dorsolumbar spine were normal. Sputum examination was negative for pyogenic organism and acid-fast bacilli. High resolution computed tomography (HRCT) of the chest showed bilateral extensive bronchiectasis (Figure 3). Tracheobronchomalacia and tracheal stenosis were excluded on virtual bronchoscopy.

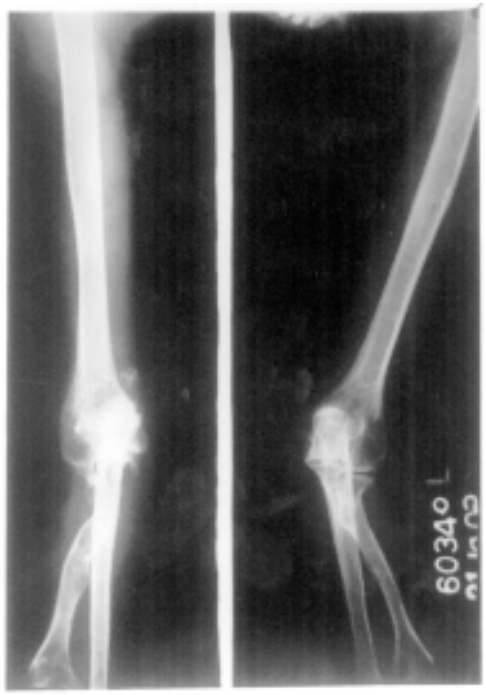

Figure 2. Radiograph of both elbows showing deformity and bowing of both radii which is more on right side and proximally with widened intraosseous space. Exuberant outgrowths are seen along medial and inferior surface of humerus.

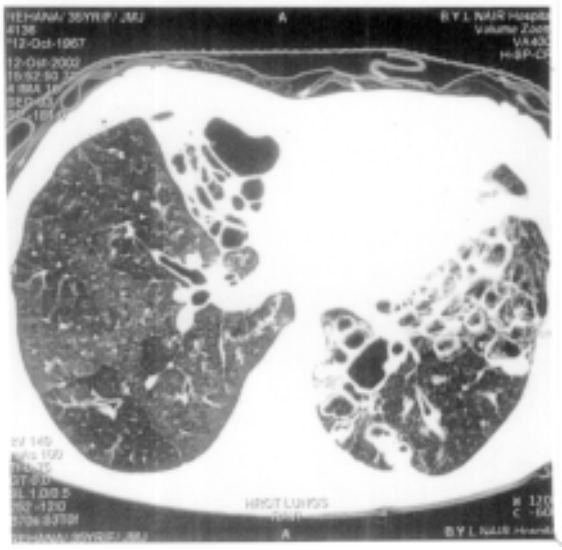

Figure 3. High resolution computed tomography (HRCT) scan of chest showing bilateral extensive bronchiectasis.

Arterial blood gas estimation showed pH 7.442, pCO_2 50.9 mmHg, pO_2 61.9 mmHg, HCO_3 34.2 mmol/L and arterial oxygen saturation (SpO_2) 88 percent. Two-dimensional echocardiography

showed pulmonary hypertension with pulmonary artery pressure of 38 mmHg. Enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) was positive. Serum immunoglobulins, IgA and IgG were elevated to 7.02 g/L (normal 0.7 to 4 g/L) and 20.57 g/L (normal 7 to 16 g/L) respectively, whereas IgM 1.8 g/L (normal 0.4 to 2.3 g/L) was within normal limits. The patient was subjected to an overnight limited sleep study to assess cardio-respiratory variables, using Densa DMS 200 (M/s Ferraris Medical Limited, U.K). The parameters recorded included airflow with oronasal flow sensors, snoring by microphone, oxygen saturation by pulse oxymetry, thoraco-abdominal movements and body position by sensors. Second night study was done by using auto titration nasal continuous airway pressure (CPAP). Baseline sleep study showed apnoea hypopnoea index (AHI) of 19 with minimum saturation of oxygen as 85%, all of which were obstructive events, corrected with mean CPAP pressure of 10 cm of H_2O. Patient was treated symnptomatically with bronchodilators and postural drainage and was prescribed CPAP.

DISCUSSION

Skeletal dysplasia are a heterogeneous group of more than 200 disorders, characterised by abnormalities of cartilage and bone growth leading to abnormal and disproportionate shape and size of the skeleton[1]. Acromesomelic dysplasias are a type of skeletal dysplasia that as a group, disproportionately affect the middle and distal segments of the limbs (forearms, forelegs, hands and feet). There are three forms of acromesomelic dysplasia: *(i)* Maroteaux type (AMDM); *(ii)* Hunter-Thompson type; and *(iii)* Grebe type. Maroteaux type[2] is an autosomal recessive skeletal disorder that affects the limbs and the spine. Newborns affected with AMDM generally have normal weight, length, and head circumference, but can have short appearing limbs. In Hunter-Thompson[6] type, adult height is about 120 cm. The trunk is normally proportioned. The facial appearance is normal, with head circumference, and intelligence is normal. The upper and lower limbs are markedly shortened with the middle and distal segments more affected than the proximal segments. Movements of all the large joints are limited with frequent dislocations. The patients sometimes walk on their knees. Fingers are generally short and of unequal length, but are generally symmetric between both hands. The lower limbs are more affected than the upper limbs. In Grebe type[6] of acromesomelic dysplasia, dwarfism is present at birth with adult height below 100 cm. While the axial skeleton is normal there is severe hypomelia with increasing severity in a proximodistal gradient. Our patient probably had Hunter-Thompson type of dysplasia as axial skeletal was spared seen in Maroteaux type and distal segment was more affected than the proximal which is seen in Grebe type.

In resource poor seetings, the World Health Organisation (WHO)[7] recommends using the TLC as a surrogate marker for the $CD4^+$ T-cell count and recommends initiating antiretroviral therapy (ART) in WHO stage II and III disease when accompanied by a TLC of less than 1200 cells/mm^3. Our patient had symptoms of bronchiectasis since childhood, had no opportunistic infections and her surrogate lymphocyte count was more than 1200 cells/mm^3, HIV seropositivity was considered as a co-incidental finding most likely related to blood transfusion in the past. Respiratory complications in the acromesomelic type dysplasia is not reported in the literature. Bronchiectasis in other types of skeletal dysplasia is due to dysgammaglobulinaemia leading to severe pulmonary infection[1]. Dysgammaglobulinaemia in the form of deficiency of subtype IgG could not be ruled out. Our patient also had obstructive sleep apnoea, which is reported in other types of skeletal dysplasia but not described in the acromesomelic variety.

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BOOK REVIEW

Wolf-Heidegger's Atlas of Human Anatomy

Edited by: Dr Petra Kopf-Maier; Published by: S. Karger AG, Basel, Switzerland;
Edition: 6th completely revised and enlarged, 2004 (Vol. 1 & 2); Hardcover;
Price: CHF150.00/EUR 89.00; ISBN 3-8055–7664–1

[Vol. 1: XX+374; Illustrations: 643 (510 in colour); Price: CHF 90.00 / EUR 49.00; ISBN 3-8055-7662-5]
[Vol. 2: XXII+514; Illustrations: 927 (736 in colour); Price: CHF 90.00 / EUR 49.00; ISBN 3-8055-7663-3]

[Indian J Chest Dis Allied Sci 2005; 47: 135]

The 6th Edition of *Wolf-Heidegger's Atlas of Human Anatomy* is a modifed version of earlier editions with emphasis on clinically relevant illustrations. This enables the reader to correlate the clinical findings easily with anatomical and topographical situations. The anatomical drawings are coloured. The major advantage of this book is the inclusion of x-ray plates and radiological sections (computed tomogram and magnetic resonance images) side by side with the anatomical drawings for comparison. All anatomical structures in this atlas are given according to the 1998 issue of the *Terminologia Anatomica*. Both English and German language notes are provided with each illustration. The atlas is printed in two volumes. The Volume 1 includes systemic anatomy, body wall, upper limbs and lower limbs. The Volume-2 includes head and neck, thoracic viscera, abdomen and pelvic viscera, pelvic floor and external genetalia, central nervous system, visual organs and orbital cavity, and vestibulo-cochlear organ. At the end of each volume, alphabetical index of commonly used eponyms is provided. This book is printed on acid-free paper with excellent quality of illustrations. As the Atlas of Human Anatomy is completely revised with excellent quality of illustrations this, book will be of very great help to the students of surgery and medicine during their clinical training programmes to understand the anatomical features with clinical correlation. Volume 2 includes sections which will be of interest of dental students as well. This Atlas will be an asset not only to anatomists, but also to surgeons and physicians and should be added to the Libraries of Medical Schools.

V.K. Vijayan
Editor-in-Chief

BOOKS RECEIVED

Atlas of Chest and TB X-rays

Editor: Dr O.A. Sarma; Published by: Paras Medical Publishers, Hyderabad;
Edition: 2nd, 2004; Pages: 158; Price: Rs.295.00; ISBN 81-8191-060-5.

Principles of Emergency Medicine

Editors: Dr Sanjeev Bhoi and Dr Ashish Goel; Published by: Paras Medical Publishers, Hyderabad;
Edition: First, 2005; Pages: 622; Price: Rs.275.00; ISBN 81-8191-087-7.

Doctors Do Cry

Editor: Dr Ashish Goel; Published by: Paras Medical Publishers, Hyderabad;
Edition: First, 2005; Pages: 170; Price: Rs.150.00; ISBN 81-8191-086-9.

ABSTRACTS' SERVICE

Indoor Air Pollution and Airway Disease

G. Viegi, M. Simoni, A. Scognamiglio, S. Baldacci, F. Pistelli, L. Carrozzi and I. Annesi-Maesano

*The International Journal of Tuberculosis and Lung Diseases 2004; **8**:1401-15*

Scientific interest in indoor pollution has been increasing since the second half of the 1980s. Growing scientific evidence has shown that because people generally spend the majority of their time indoors, indoor pollution plays a significant role in affecting health and is thus an important health issue. Indoor environments include dwellings, workplaces, schools and day care centres, bars, discotheques and vehicles. Common indoor pollutants are environmental tobacco smoke, particulate matter, nitrogen dioxide, carbon monoxide, volatile organic compounds and biological allergens. In developing countries, relevant sources of indoor pollution include biomass and coal burning for cooking and heating. Concentrations of these pollutants can be many times higher indoors than outdoors. Indoor air pollution may increase the risk of irritation phenomena, allergic sensitisation, acute and chronic respiratory disorders and lung function impairment. Recent conservative estimates have shown that 1.5–2 million deaths per year worldwide could be attributed to indoor air pollution. Approximately 1 million of these deaths occur in children aged under 5 years due to acute respiratory infections, and significant proportions of deaths occur due to chronic obstructive pulmonary disease and lung cancer in women. Today, indoor air pollution ranks tenth among preventable risk factors contributing to the global burden of disease. Further research is necessary to better evaluate the respiratory health effects of indoor pollution and to implement protective programmes for public health.

Extended Work Shifts and the Risk of Motor Vehicle Crashes Among Interns

Laura K. Barger, Brian E. Cade, Najib T. Ayas, John W. Cronin, Bernard Rosner, Frank E. Speizer, and Charles A. Czeisler for the Harvard Work Hours, Health, and Safety Group

*The New England Journal of Medicine 2005; **352**: 125-34*

Background. Long work hours and work shifts of an extended duration (≥ 24 hours) remain a hall-mark of medical education in the United States. Yet their effect on health and safety has not been evaluated with the use of validated measures.

Methods. We conducted a prospective nationwide, Web-based survey in which 2737 residents in their first postgraduate year (interns) completed 17,003 monthly reports that provided detailed information about work hours, work shifts of an extended duration, documented motor vehicle crashes, near-miss incidents, and incidents involving involuntary sleeping.

Results. The odds ratios for reporting a motor vehicle crash and for reporting a near-miss incident after an extended work shift, as compared with a shift that was not of extended duration, were 2.3 (95 percent confidence interval, 1.6 to 3.3) and 5.9 (95 percent confidence interval, 5.4 to 6.3), respectively. In a prospective analysis, every extended work shift that was scheduled in a month increased the monthly risk of a motor vehicle crash by 9.1 percent (95 percent confidence interval, 3.4 to 14.7 percent) and increased the monthly risk of a crash during the commute from work by 16.2

percent (95 percent confidence interval, 7.8 to 24.7 percent). In months in which interns worked five or more extended shifts, the risk that they would fall asleep while driving or while stopped in traffic was significantly increased (odds ratios, 2.39 [95 percent confidence interval, 2.31 to 2.46] and 3.69 [95 percent confidence interval, 3.60 to 3.77], respectively).

Conclusions. Extended-duration work shifts, which are currently sanctioned by the Accreditation Council for Graduate Medical Education, pose safety hazards for interns. These results have implications for medical residency programs, which routinely schedule physicians to work more than 24 consecutive hours.

The WHO/IUATLD Diagnostic Algorithm for Tuberculosis and Empiric Fluoroquinolone Use: Potential Pitfalls

T.R. Sterling

*The International Journal of Tuberculosis and Lung Diseases 2004; **8**: 1396-1400*

According to the current WHO/IUATLD diagnostic algorithm for tuberculosis, to establish the diagnosis of smear-negative pulmonary disease, patients should first demonstrate no clinical response to a course of broad-spectrum antibiotics. The fluoroquinolones have broad-spectrum activity against respiratory pathogens and are generally considered first-line therapy for the treatment of community-acquired pneumonia; they also have bactericidal activity *Mycobacterium tuberculosis*. Of note, empiric fluoroquinolone monotherapy has been associated with delays in the initiation of appropriate anti-tuberculosis therapy, and also resistance in *M. tuberculosis*. Delays in the diagnosis and treatment of tuberculosis are associated with increased morbidity and mortality. Resistance to fluoroquinolones in *M. tuberculosis* could limit the use of this potentially first-line class of anti-tuberculosis agents. The WHO/IUATLD diagnostic criteria for smear-negative tuberculosis should be revised to ensure that fluoroquinolones are not used inappropriately and that the detrimental effects of empiric fluoroquinolone monotherapy in tuberculosis patients are avoided.

The Relationship Between Cigarette Smoking and Quality of Life After Lung Cancer Diagnosis

Yolanda I. Garces, Ping Yang, Julia Parkinson, Xinghua Zhao, Jason A. Wampfler, Jon O. Ebbert and Jeff A. Sloan

*Chest 2004; **126**: 1733-41*

Study objective. To describe the relationship between cigarette smoking and quality of life (QOL) among lung cancer survivors as measured by the lung cancer symptom scale (LCSS).

Design and setting. The LCSS was mailed to eligible patients (1,506 patients) between 1999 and 2002. LCSS scores (total and individual QOL components) were compared among different groups of cigarette smokers via univariate independent group testing and multivariate linear models. The modeling process examined group differences adjusted for age, gender, stage, and time of LCSS assessment. LCSS scores were transformed onto a scale of 0 to 100 points in which higher LCSS scores corresponded to a lower QOL. A 10-point difference between groups was defined *a priori* as being clinically significant.

Results. At the time of lung cancer diagnosis, 18% of the patients were never-smokers, 58% were former smokers, and 24% were current smokers. Among survey respondents completing the LCSS at follow-up assessment (1,028 respondents), the mean age was 65.2 years (SD, 10.8 years) and 45% were women. Thirty percent of baseline current smokers continued to smoke at the time of the follow-up assessment (*i.e.*, persistent smokers). The adjusted mean total LCSS scores for never-smokers and persistent smokers were 17.6 (SD, 4.02) and 28.7 (SD, 5.09), respectively ($p<0.0001$). Seven of the individual LCSS QOL components (*ie*, appetite, fatigue, cough, shortness of breath, lung cancer symptoms, illness affecting normal activities, and overall QOL) were clinically and statistically ($p<0.001$) different between never-smokers and persistent smokers. No clinically significant differences were noted for pain or hemoptysis. Former smokers had intermediate LCSS scores. No dose-response trends were observed between the number of packs of cigarettes smoked per day or the total number of pack-years smoked and the adjusted scores.

Conclusion. The hypothesized relationship between smoking status and QOL was supported by this correlational study. Our findings suggest that persistent cigarette smoking after a lung cancer diagnosis negatively impacts QOL scores.

The Impact of Smoking Status on the Behavior and Survival Outcome of Patients with Advanced Non-small Cell Lung Cancer: A Retrospective Analysis

Chee-Keong Toh, Ee-Hwee Wong, Wan-Teck Lin, Swan-Swan Leong, Kam-Weng Fong, Joseph Wee and Eng-Huat Tan

*Chest 2004; **126**: 1750-56*

Study objectives. There are fundamental differences in characteristics between smokers and nonsmokers with non-small cell lung cancer (NSCLC). We aim to study the impact of smoking status on the behavior of the disease, and to identify differences in outcome between the two groups.

Design. A retrospective analysis was done of patients with NSCLC seen during the period from January 1999 to August 2002. Clinical characteristics, survival outcome, and response to treatment were reviewed and compared between the smokers and nonsmokers.

Setting. Department of Medical Oncology, National Cancer Center.

Results. Of 317 patients analyzed, 117 patients (36.3%) were nonsmokers. Among the nonsmokers, 74.5% had adenocarcinoma and 73.9% were women. The smokers had poorer performance status, reported more weight loss, and had a higher mean age at diagnosis of almost 8 years than nonsmokers. Once hundred eighty-seven patients (59%) had died as of December 31, 2002. The nonsmokers had a longer median survival, although this was not statistically significant. There were no statistically significant differences in survival and response to chemotherapy between the two groups after adjusting for known prognostic factors.

Conclusions. Despite the known differences in mutational spectra and clinical characteristics between smokers and nonsmokers with NSCLC, no differences in terms of response to chemotherapy and survival outcome were observed. This could imply that this disease is equally aggressive in these two groups. More research is needed to further delineate and characterize the differences between these two etiologically different forms of NSCLC.

Loss of Bone Density with Inhaled Triamcinolone in Lung Health Study II

Paul D, Scanlon, John E. Connett, Robert A. Wise, Donald P. Tashkin, Thelma Madhok, Melissa Skeans, Paul C. Carpenter, William C. Bailey, A. Sonia Buist, Michael Eichenhorn, Richard E. Kanner, Gail Weinmann, and the Lung Health Study Research Group

*American Journal of Respiratory and Critical Care Medicine 2004; **170**: 1302-9*

Inhaled glucocorticosteroids (ICS) are commonly prescribed for chronic obstructive pulmonary disease. No adverse effect on bone mineral density (BMD) has been proven. In a randomized doubleblind, placebo-controlled trial at seven centers in North America, we recruited 412 current smokers or recent quitters with mild to moderate chronic obstructive pulmonary disease. They used inhaled triamcinolone acetonide, 600 mcg, or placebo, twice daily. We measured femoral neck and lumbar spine BMD at baseline and after 1 and 3 years, and serum osteocalcin at baseline, 3 months, 1 year, and 3 years. After 3 years, BMD at the femoral neck decreased 1.78% more with ICS than with placebo ($p<0.001$). More participants in the ICS group experienced 6% or more loss of femoral neck BMD ($p=0.002$). Lumbar spine BMD increased in the placebo group by 0.98% but decreased by 0.35% in the ICS group (a difference of 1.33%, $p=0.007$). Changes in osteocalcin did not correlate with changes in BMD. Fractures, lost height, or osteoporosis diagnoses were not increased among ICS users compared with placebo users. In summary, the use of inhaled triamcinolone acetonide was associated with loss of BMD at the femoral neck and lumbar spine after 3 years of treatment.

Contributions of High Mobility Group Box Protein in Experimental and Clinical Acute Lung Injury

Hiroshi Ueno, Tomoyuki Matsuda, Satoru Hashimoto, Fumimasa Amaya, Yoshihiro Kitamura, Masaki Tanaka, Atsuko Kobayash, Ikuro Maruyama, Shingo Yamada, Naoki Hasegawa, Junko Soejima, Hidefumi Koh and Akitoshi Ishizaka

*American Journal of Respiratory and Critical Care Medicine 2004; **170**: 1310-16*

This study was performed to examine the putative role of high mobility group box (HMGB) protein in the pathogenesis of acute lung injury (ALI), Observations were made (1) in 21 patients who were septic with ALI and 15 patients with normal lung function and (2) in a mouse model 24 hours after intratracheal instillation of lipopolysaccharide (LPS). The concentrations of HMGB1 were increased in plasma and lung epithelial lining fluid of patients with ALI and mice instilled with LPS. LPS-induced ALI was mitigated by anti-HMGB1 antibody. Although this protein was not detected in the plasma of control humans or mice, the concentrations of HMGB1 in lung epithelial lining fluid or in bronchoalveolar lavage fluid were unexpectedly high. The nuclear expression of HMGB1 was apparent in epithelial cells surrounding terminal bronchioles in normal mice, whereas its nuclear and cytoplasmic expression was observed in alveolar macrophages in LPS-instilled mice. Lung instillation of HMGB 2 did not cause as much inflammation as HMGB1. Extracellular HMGB1 may play a key role in the pathogenesis of clinical and experimental ALI. However, its expression in normal airways is noteworthy and suggests that it also plays a physiologic role in the lung.

Surgical Resection of Limited Disease Small Cell Lung Cancer in the New Era of Platinum Chemotherapy: Its Time Has Come

Malcolm V. Brock, Craig M. Hooker, James E. Syphard, William Westra, Li Xu, Anthony J. Alberg, David Mason, Stephen B. Baylin, James G. Herman, Rex C. Yung, Julie Brahmer, Charles M. Rudin, David S. Ettinger and Stephen C. Yang

*The Journal of Thoracic and Cardiovascular Surgery 2005; **129**: 64-72*

Objective. Although resection is not the standard of care in treating small cell lung cancer, new platinum drugs and modern staging have allowed the role of surgery to be reevaluated.

Methods. We reviewed our institutional experience of 1415 patients with small cell lung cancer from 1976 to 2002 among whom 82 (6%) underwent surgery with curative intent.

Results. Median age at surgery was 62 years, and small cell lung cancer of mixed morphology represented 14 of 82 (17%). Treatment consisted of surgery alone in 11% of cases (9/82), surgery with neoadjuvant therapy in 22% (18/82), and surgery with adjuvant therapy in 55% (45/82). Prophylactic cranial irradiation was given to 23% (19/82). The 5-year survival of the entire cohort was 42%. The 5-year survival of patients receiving adjuvant chemotherapy (n=41) was significantly different according to whether patients had received platinum or nonplatinum regimens (68% vs 32.2%, *P=.04)*. Among patients with stage I disease who received adjuvant chemotherapy (n=24), the 5-year survivals for patients receiving platinum and nonplatinum chemotherapy were 86% and 42%, respectively (*P<.02)*. If patients who received either neoadjuvant or adjuvant therapy (n=56) were considered, the 5-year survival was significantly better for platinum than for nonplatinum chemotherapy (62% vs 36% *P=.05)*. The 5-year survival was also better for those undergoing lobectomies (n=52) than for those with limited resections (n=15, 50% vs 20% *P=.03)*. Survival outcome also differed by gender, with female patients having a 5-year survival advantage over male patients (60% vs 28%, *P=.004)*.

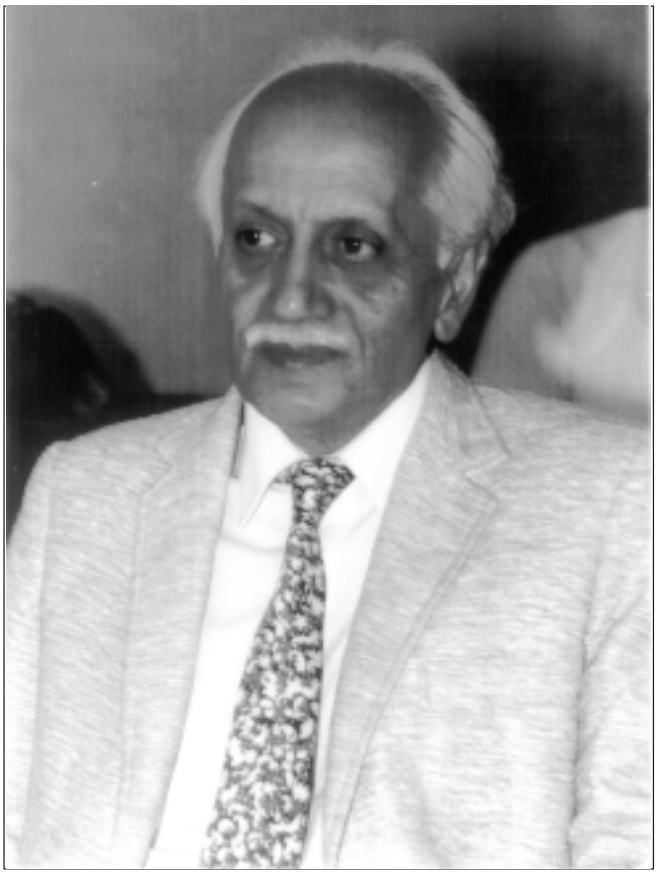
Conclusion. These results support a reevaluation of the role of surgery in the multimodality therapy for small cell lung cancer, which currently includes only radiotherapy and chemotherapy.

Some Forthcoming Scientific Events

Name of the Event [Venue and Date]	Secretariat
Ist National Conference of the Indian Society for Study of Lung Cancer (NALCCON-2005) [PGI, Chandigarh; April 2-3, 2005]	Dr D. Behera, Organising Secretary and Professor, Department of Pulmonary Medicine, PGI, Chandigarh-160 012 Phone: (Off.): 91-0172-2747585-94 Extn 6822 (Resi.): 91-0172-2715357 Fax: 91-0172-2747759 E-mail: dbehera@glide.net.in
National Symposium on Influenza: Epidemiology and Control [V.P. Chest Institute, Delhi; April 5, 2005]	Dr V.K. Vijayan Director and Chairman Organising Committee Phone: (Off.): 91-11-27666180 (Resi.): 91-11-27667027 Fax: 91-11-27667420 E-mail: vijayanvk@hotmail.com and Dr Madhu Khanna, Organising Secretary and Senior Lecturer, Department of Respiratory Virology, V.P. Chest Institute, University of Delhi, Delhi-110 007 Phone: (Off.): 91-11-27667441, 27667667, 27667102 Extn 132 (Resi.): 91-11-25841210 E-mail: madhukhanna2004@rediffmail.com
Vth CME: National Update on COPD [V.P. Chest Institute, Delhi; April 24, 2005]	Dr V.K. Vijayan Director and Chairman Organising Committee Phone: (Off.): 91-11-27666180 (Resi.): 91-11-27667027 Fax: 91-11-27667420 E-mail: vijayanvk@hotmal.com and Dr Raj Kumar, Organising Secretary Phone: (Off.): 91-11-27667102, 27667441, 27667667, Extn 144 (Resi.): 91-11-27666868 Fax: 91-11-27667420 E-mail: rajkumar_27563@yahoo.co.in
VIIth Annual Conference-cum-Workshop of the Indian Association of Mycoplasmologists [V.P. Chest Institute, Delhi; April 28-29, 2005]	Dr Mandira Varma, Organising Secretary and Senior Lecturer, Department of Microbiology V.P. Chest Institute, University of Delhi, Delhi-110 007 Phone: 91-11-27667667, 27667102, 27667441 Extn 117 Fax: 91-11-27667420 E-mail: mandirav@rediffmail.com
National Conference on Pulmonary Diseases (NAPCON-2005) *(VIIth Joint Conference of the Indian Chest Society and National College of Chest Physicians (India)* [Science City, Kolkata; November 16-20, 2005]	Dr Dhiman Ganguly, Chairman, Organising Committee, and Dr A.G. Ghoshal, Secretary, Organising Committee EKO X-Ray & Imaging Institute, 54, Jawahar Lal Nehru Road, Kolkata-700 071 Phone: 91-033-2282 8109 Extn 149 E-mail: drdganguly@yahoo.co.in/info@napcon2005.co; and agghoshal@vsnl.net Website: www.napcon2005.com

[Indian J Chest Dis Allied Sci 2005; 47: 143-145]

OBITUARY



Professor Autar Singh Paintal

(1925–2004)

Professor Autar Singh Paintal, Emeritus Editor-in-Chief of the *Indian Journal of Chest Diseases and Allied Sciences*, died on December 21, 2004 and was a global figure in the field of cardio-respiratory sensory physiology. He was born on September 24, 1925, in the ruby mining town of Mogok in Myanmar, erstwhile Burma. His father Dr Man Singh was a physician in the British Medical Services. He completed his matriculation from Lahore, and did his intermediate examination of the Punjab University from Forman Christian College. He subsequently obtained admission at King George's Medical College, Lucknow in 1943. His stay at the Medical College (1943-1948) was marked by distinction and awards, including the coveted HEWITT Gold Medal. He did his M.D. in Physiology in 1950 from K.G.'s Medical College, Lucknow.

After being appointed a lecturer in the Physiology Department of King George's Medical College, he proceeded to work for his Ph.D. degree (1952) with Prof. David Whitteridge in the Physiology Department of the Medical School in Edinburgh on a Rockefeller Fellowship. While in UK, he developed two innovative techniques in electro-physiology, which revolutionised studies on sensory physiology. The first one involved usage of liquid paraffin for immersing nerves while dissecting and recording from them. The second one was injection of chemicals into the circulation to discover 'silent' sensory visceral receptors. For his contributions, he was elected to the British Physiological Society in 1953.

After obtaining his Ph.D. he returned to India to work as a Technical Officer of the Defence Laboratories in Kanpur before taking up the post of Assistant Director at V.P. Chest Institute where he made several discoveries for which he is famous globally. From 1956-58, he was invited as Visiting Professor at Albert Einstein College of Medicine, New York, USA, University of Utah, Salt Lake City, USA and University of Gottingen, Germany. He was then offered the position of Professor of Physiology at AIIMS where he spent six years from 1958-64. It was during this period that he received his D.Sc. degree from the University of Edinburgh in 1960. In 1964, he returned to V.P. Chest Institute as the Director and stayed there till his retirement in 1990. He was the Director-General of the Indian Council of Medical Research from 1986 to 1991.

During the years 1952-1960, he discovered several sensory receptors in the viscera. These include the type B receptors of atria, the ventricular pressure receptors, the gastric stretch receptors, the mucosal mechanoreceptors of the intestines, and the pressure pain receptors of muscles. Foremost amongst the receptors discovered by him were the juxtapulmonary capillary or type J receptors which are stimulated by a rise in the interstitial fluid volume and increase in pulmonary blood flow. Their stimulation gives rise to breathlessness and termination of exercise. He described the reflex, termination of exercise as one of their most important functions–providing a protective reflex to humans and animals against excessive pulmonary pressures. He and his collaborators showed that these receptors are also stimulated by increased blood flow, as in exercise and that stimulation of J receptors produced respiratory sensations leading to dry cough. His work on the conduction and block in mammalian nerves gave the electrophysiologists, a tool to enable them to distinguish between the myelinated and non-myelinated nerve fibres. He also demonstrated that the Head's Paradoxical reflex was an artefact. His contributions came to be described as having opened a new era in Physiology with Cornellie Heymans and Eric Neil coining the terms "Pre-Paintal' *versus* "Post-Paintal" while referring to the impact of his discoveries. In his own view, his greatest contribution to science in India apart from his discoveries has been the formation of the Society of Scientific Values, which he helped to establish and served as its first President. This Society, the first of its kind in the world, has as its main objective, amongst others, to promote integrity, objectivity and ethical values in the pursuit of science.

He was elected to the Fellowship of the Royal Society of Edinburgh in 1966, followed by an election to the National Academy of Medical Sciences, and the Indian National Science Academy. In 1981, he was elected to the Royal Society (U.K.) and was the first Indian medical scientist to be so honoured. An honorary membership of the Physiological Society (U.K.) and the American Physiological Society followed soon after as did an Honorary Fellowship of the Royal College of Physicians. His outstanding scientific contributions won him several National Awards and Honours, *viz.* Dr B.C. Roy Award (1973), Medical Council Silver Jubillee Research Award (1979), Barclay Medal (1982), Rameswar Birla National Award (1982), First Jawaharlal Award in Science (1983), Acharya J.C. Bose Medal (1985), Silver Jubilee Award, AIIMS (1986), C.V. Raman Award (1995), Jawaharlal Nehru Birth Centenary Award (2002). The President of India bestowed on him the coveted honour of **"Padma Vibhushan"** in 1986. He was elected as a member of the International Council of Physiological Sciences in 1997 and re-elected for another term upto 2005.

Based on his recent discoveries, the Department of Science and Technology set up a Centre for Visceral Mechanisms at the Vallabhbhai Patel Chest Institute so as to intensify and extend the work on dyspnoea (breathlessness) and exercise limitation that arise reflexly by stimulation of J receptors. He continued as the Programme Director of the centre until his death.

(Dr V.K. Vijayan)
Editor-in-Chief

OBITUARY

Dr Madhu Sudan Agnihotri

With deep sense of sorrow, the Secretary informs that Professor Madhu Sudan Agnihotri, Founder Fellow and Past President of the National College of Chest Physians (India) left for heavenly abode. We all deeply mourn the sudden and untimely demise of Professor Agnihotri and pray to God for peace to the departed soul.

Brief achievements of Professor Madhu Sudan Agnihotri are given below:

Ex-Professor and Head, Department of TB and Chest Diseases, K.G. Medical College, Lucknow
Ex-President of the National College of Chest Physicians (India)
Ex-President of the Indian College of Allergy and Applied Immunology
Ex-President of the Tuberculosis Association of India
Receipient of B.C. Roy Award
Established Asthma Research Cell at KGMC, Lucknow
Established Asthma Care Foundation at Lucknow
Established Allergy Clinic at KGMC, Lucknow

Professor Agnihotri was an excellent Teacher, Research worker and good Administrator. He was a source of encouragement and inspiration to most of us.

A 2-minute silence was observed at the Governing Council and General Body meetings of the NCCP (I) at Ahmedabad to pay our respect to a nobel soul.

Sd/-
Secretary, NCCP(I)

OBITUARY

Dr Dilip Kumar Patel

With deep sense of sorrow, the Secretary informs that Dr Dilip Kumar Patel, young, energetic life Member of the National College of Chest Physicians (India), left for heavenly abode. We all mourn the sudden and untimely demise of Dr Patel.

Brief achievements of Dr Dilip Kumar Patel are given below:

Ex-Professor of BT Medical College, Ahmedabad
Ex-Examiner and Chairman, Gujarat University
Ex-Examiner, Udaipur and Mumbai Universities
Chairman, Scientific Committee, NAPCON-2004

A 2-minute silence was observed at the Governming Council and General Body meetings of the NCCP (I) at Ahmedabad to pay our respect to the departed soul.

Sd/-
Secretary, NCCP(I)

[Indian J Chest Dis Allied Sci 2005; 47: 146-152]

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General. Manuscripts must be typewritten, double-spaced with wide margin on A-4 size good quality bond paper. Each of these segments of the manuscript should begin on a new page: title page; abstract; introduction; references; legends; tables.

I. *Title Page.* This should be as concise and as informative as possible. List (*i*) title; (*ii*) the initials followed by the last name of each author; (*iii*) the name of the department(s) and institution(s) to which the work should be attributed; (*iv*) the name and address of the author to whom queries, proofs and requests for reprints should be sent; and (*v*) a short running title (not exceeding 5-6 words).

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III. *Introduction.* It should commence on separate page and should briefly review the current state of knowledge strictly concerning the topic of the paper. It should also make a clear statement on the reasons for undertaking the study being reported and what it hoped to achieve. No mention should be made of the

results obtained or conclusions drawn.

IV. *Material and Methods.* The material (patients, experimental animals, etc.) used for making observations must be described along with all other relevant information. The methods used in the study should be described, giving sufficient information to permit the work to be repeated. If a generally accepted technique has been used, only a reference to that is enough. If, however, such a technique has been modified by the workers, the manner in which this has been done should be clearly stated. If statistical analysis of the data has been done, the methods used for analysis should be specified.

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VI. *Discussion*. This should be limited to significance of results obtained and what can and what cannot be concluded and why. It should not be a repetition of the findings already given under 'Results'. Results should be discussed in the light of others' work in the field. Speculative and purely theoretical discussion to which results presented are not related will not be accepted.

VII. *Acknowledgements*. Acknowledgement should be brief and made specific for scientific / technical assistance and financial supports in the form of grants / drugs / equipment only and for not providing routine departmental facilities and for help in the preparation of manuscript (including typing / secretarial assistance).

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Articles in Journals

1. *Standard journal article*

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347: 284-7.

More than six authors:

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, *et al.* Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res* 2002; 935 (1-2): 40-6.

2. *Article published electronically ahead of the print version*

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. *Blood* 2002 Nov 15; 100(10): 3828-31. Epub 2002 July 5.

3. Volume with supplement

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short-and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; 42 Suppl 2: S93-9.

4. *Issue with supplement*

Glauser TA. Integrating clinical trial data into clinical practice. *Neurology* 2002; 58 (12 Suppl 7): S6-12.

5. *Type of article indicated as needed*

Tor M, Turker H. International approaches to the

prescription of long-term oxygen therapy [letter]. *Eur Respir J* 2002; 20(1): 242.

Lofwall MR, Strain EC, Brooner RK, Kindbom KA, Bigelow GE. Characteristics of older methadone maintenance (MM) patients [abstract]. *Drug Alcohol Depend* 2002; 66 Suppl 1: S105.

6. *Volume with part*

Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. *Int J Psychoanal* 2002; 83 (Pt 2): 491-5.

7. *Issue with part*

Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumours. *J Vasc Interv Radiol.* 2002; 13(9 Pt 1): 923-8.

8. *Issue with no volume*

Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop* 2002; (401): 230-8.

9. *No volume or issue*

Outreach: bringing HIV-positive individuals into care. *HRSA Careaction* 2002 Jun: 1-6.

10. *Pagination in roman numerals*

Chadwick R, Schuklenk U. The politics of ethical consensus finding. *Bioethics* 2002; 16(2): iii-v.

11. *Organization as author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; 40(5): 679-86.

12. *Both personal authors and an organization as author* (This example does not conform to NISO standards).

Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; 169(6): 2257-61.

13. *No author given*

21st century heart solution may have a sting in the tail. *BMJ* 2002; 325(7357): 184.

14. *Article containing retraction*

Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. *J Clin Psychiatry* 2002; 63(2): 169. Retraction of: Feifel D, Moutier CY, Perry W. *J Clin Psychiatry* 2000; 61(12): 909-11.

15. *Article retracted*

Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. *J Clin Psychiatry* 2000; 61(12): 909-11. Retraction in: Feifel D, Moutier CY, Perry W. *J Clin Psychiatry* 2002; 63(2): 169.

16. *Article republished with corrections*

Mansharamani M, Chilton BS. The reproductive importance of P-type ATPases. *Mol Cell Endocrinol* 2002; 188(1-2): 22-5. Corrected and republished from: *Mol Cell Endocrinol* 2001; 183(1-2): 123-6.

17. *Article with published erratum*

Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. *Clin Ther* 2000; 22(10): 1151-68; discussion 1149-50. Erratum in : *Clin Ther* 2001; 23(2): 309.

18. *Article not in English*

(Note: NLM translates the title into English, encloses the translation in square brackets, and adds an abbreviated language designator.)

Ellingsen AE, Wilhelmsen I. *Sykdomsangst blant medisin-og jusstudenter. Tidsskr Nor Laegeforen* 2002; 122(8): 785-7.

Personal Communication

Name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

Unpublished Material

19. *In press*

(Note: NLM prefers “forthcoming” because not all items will be printed.)

Tian D, Araki H, Stahl E, Bergelson J, Kreitman

M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA*. In press 2002.

Books and Other Monographs

20. *Chapter in a book*

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumours. In: Vogelstein B, Kinzler KW, editors. *The Genetic Basis of Human Cancer*. New York: McGraw-Hill. 2002; pp 93-113.

21. *Conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In : Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: *Proceedings of the 5th European Conference on Genetic Programming;* 2002 Apr 3-5; Kinsdale Ireland. Berlin: Springer. 2002; pp 182-91.

22. *Personal author(s)*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. *Medical Microbiology;* 4th ed. St. Louis: Mosby. 2002.

23. *Editor(s), compiler(s) as author*

Gilstrap LC (3rd), Cunningham FG, VanDorsten JP, editors. *Operative Obstetrics*. 2nd ed. New York: McGraw-Hill. 2002.

24. *Author(s) and editor(s)*

Breedlove GK, Schorfheide AM. *Adolescent Pregnancy*. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

25. *Organization(s) as author*

Royal Adelaide Hospital; University of Adelaide, Department of Clinical Nursing. *Compendium of Nursing Research and Practice Development, 1999-2000*. Adelaide (Australia): Adelaide University; 2001.

26. *Conference proceedings*

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. *Proceedings of the 5th Germ Cell Tumour Conference;* 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

27. *Scientific or technical report*

Issued by funding / sponsoring agency:

Yen GG (Oklahoma State University, School of Electrical and Computer Engineering, Stillwater, OK). Health monitoring on vibration signatures. Final report. Arlington (VA): Air Force Office of Scientific Research (US), Air Force Research Laboratory; 2002 Feb. Report No.: AFRLSRBLTR020123. Contract No.: F496209810049.

Issued by performing agency:

Russelll ML, Goth-Goldstein R, Apte MG, Fisk WJ. Method for measuring the size distribution of airborne Rhinovirus. Berkeley (CA): Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; 2002 Jan. Report No.: LBNL49574. Contract No.: DEAC0376SF00098. Sponsored by the Department of Energy.

28. *Dissertation*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

29. *Patent*

Pegedas AC, inventor; Ancel Surgical R& D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1.

Other Published Material

30. *Newspaper article*

Tynan T. Medical improvements lower homicide rate: study sees drop in assault rate. *The Washington Post*. 2002 Aug 12; Sect. A:2 (col. 4).

31. *Audiovisual material*

Chason KW, Sallustio S. Hospital preparedness for bioterrorism [videocassette]. Secaucus (NJ): Network for Continuing Medical Education; 2002.

32. *Legal Material*

Public law:

Veterans Hearing Loss Compensation Act of 2002, Pub.L.No. 107-9, 115 Stat. 11 (May 24, 2001).

Unenacted bill:
Healthy Children Learn Act, S. 1012, 107th Cong., 1st Sess. (2001).

Code of Federal Regulations:
Cardiopulmonary Bypass Intracardiac Suction Control, 21 C.F.R. Sect. 870.4430 (2002).

Hearing:
Arsenic in Drinking Water: An Update on the Science, Benefits and Cost: Hearing Before the Subcomm. on Environment, Technology and Standards of the House Comm. on Science, 107th Cong., 1st Sess. (Oct. 4, 2001).

33. Map

Pratt B, Flick, P, Vynne C, cartographers. Biodiversity hotspots [map]. Washington: Conservation International; 2000.

34. Dictionary and similar references

Dorland's Illustrated Medical Dictionary. 29th ed. Philadelphia: W.B. Saunders; 2000. Filamin; p. 675.

Electronic Material

35. CD-ROM

Anderson SC, Poulsen KB. *Anderson's Electronic Atlas of Hematology* [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

36. Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs* [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6) : [about 3 p.]. Available from: http: // www.nursingworld.org / AJN / 2002 / june / Wawatch.htm

37. Monograph on the Internet

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http: // www.nap.edu / books / 0309074029 / html / .

38. Homepage / Web site

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http: // www.cancer-pain.org /.

39. Part of a homepage / Web site

American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: http // www.ama-assn.org / ama / pub / category1736.html.

40. Database on the Internet

Open database:
Who's Certified [database on the Internet]. Evanston (IL): The American Board of Medical Specialists. c2000-[cited 2001 Mar 8]. Available from: http: // www.abms.org / newsearch.asp

Closed database:
Jablonski S. Online Multiple Congential Anomaly / Mental Retardation (MCA / MR) Syndromes [database on the Internet]. Bethesda (MD): National Library of Medicine (US). c1999 [updated 2001 Nov 20; cited 2002 Aug 12]. Available from: http: // www.nlm.nih.gov / mesh / jablonski / syndrome_title.html

41. Part of a database on the Internet

MeSH Browser [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2002 - [cited 2003 Jun 10]. Meta-analysis; unique ID: D015201; [about 3 p.]. Available from: http: //www.nlm.nih.gov / mesh / MBrowser.html Files updated weekly.

MeSH Browser [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2002 - [cited 2003 Jun 10]. Meta-analysis; unique ID: D015201; [about 3 p.]. Available from: http: //www.nlm.nih.gov / mesh / MBrowser.html Files updated weekly.

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