Awake Abnormalities of Control of Breathing and of the Upper Airway

Occurrence in Healthy Older Men with Nocturnal Disordered Breathing

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We hypothesized that preexisting diminished chemical control of breathing and narrowing of the upper airway are associated with sleep-related disordered breathing (SRDB) in healthy older men. Twenty-six subjects, aged 55 to 70, were studied. An SRDB episode was a decrease in arterial oxygen saturation (SaO₂) of at least 4 percent. Some of these episodes occurred while airflow continued (i.e., nonapneic episodes), and the rest occurred with apnea. Sixteen subjects had >12 SRDB episodes per hour of sleep (SRDB subjects) and ten subjects had <8 episodes per hour (controls). During waking, the mean hypcapnic ventilatory response was lower, and the mean supine nasal airway resistance (SNAR) was higher in SRDB subjects than in control subjects. During waking, 12 of 16 SRDB subjects had one or more respiratory abnormalities: four had an elevated SNAR; four had a reduced hypercapnic response; three had a reduced hypoxic ventilatory response, and two had an abnormal flow-volume curve. Only one of ten control subjects had a respiratory abnormality (an elevated SNAR). Also, the number of SRDB episodes per hour correlated with the SNAR, and the minimum SaO₂ during sleep correlated with the magnitude of the hypercapnic response. We conclude that SRDB occurs commonly in otherwise healthy older men with preexisting abnormalities of control of breathing or of the upper airway.

The high (44 percent to 82 percent) prevalence of hypopnea, apnea, and arterial oxygen desaturation during sleep in otherwise healthy older subjects has been reported. The precise mechanisms of this sleep-related disordered breathing (SRDB) are unknown. By analogy with the sleep-apnea and Pickwickian syndromes, preexisting narrowing of the upper airway or diminished chemical control of breathing can be hypothesized to contribute to SRDB in elderly subjects.

The purpose of this study was, first, to define a group of healthy older subjects aged 55 to 70 years. Next, we studied the following in this group: (1) awake respiratory measurements including hypoxic and hypercapnic ventilatory responses, supine and upright nasal airway resistance, and inspiratory and expiratory flow-volume curves; and (2) the prevalence of SRDB as identified by episodes of arterial oxygen desaturation. Finally, we determined if correlations existed between the awake respiratory measurements and the rate and severity (i.e., the degree of desaturation) of SRDB.

Materials and Methods

Subject Population

Male military veterans, aged 55 to 70 years, were recruited as volunteers from the patient population of Sepulveda Veterans Administration Medical Center and from the local community. These volunteers were screened initially by history and physical examination, pulmonary function testing including spirometry, lung volumes, and arterial blood gas values, blood chemistry values (SMA 18), complete blood counts, and if indicated, an ECG. Subjects with abnormal pulmonary function (forced expiratory volume in 1 second [FEV₁] less than 80 percent predicted);³ with a history of cardiac, neurologic, psychiatric, renal or endocrine disease; using psychoactive drugs; with ECG abnormalities; with a current history of drinking more than 3 ounces of ethanol per week; with an arterial Pco₂ >42 or Pco₂ <65 mm Hg; with abnormal blood chemistry values or blood count or with symptoms of daytime sleepiness or any other obvious symptom or finding (except mild-to-moderate systemic hypertension or snoring) of the sleep-apnea syndrome were excluded from the study. Subjects with upper respiratory tract infections, active hay fever, or other acute nasal illnesses were also excluded from participation. Subjects were not specifically excluded because of current cigarette smoking or obesity; provided they met all other criteria. Three subjects who were current smokers and three other subjects whose weight was greater than 120 percent of ideal body weight qualified for the study. Of note, based on subsequent analyses of pulmonary function, SRDB frequency, and minimum arterial oxygen saturation during sleep, these six subjects did not differ from other qualified subjects.

Of 178 subjects screened, 26 qualified as healthy for this study. Subjects signed written, informed consent forms. Subjects using antihypertensive drugs were gradually withdrawn over a two- to three-week period in conjunction with daily blood pressure monitoring. We emphasize that none of the subjects was receiving any form of regular medication during this study. After the initial screening,
Table 1—Clinical Data (X± SEM)*

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>FEV₁ (% Pred)</th>
<th>SRDB hr</th>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>Baseline SaO₂ (%)</th>
<th>Minim SaO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>64</td>
<td>±1.4</td>
<td>176</td>
<td>±2.7</td>
<td>±5</td>
<td>±0.74</td>
<td>±2.2</td>
<td>±5</td>
<td>±1.1</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.3</td>
<td>84</td>
<td>34</td>
<td>95</td>
</tr>
<tr>
<td>SRDB</td>
<td>65</td>
<td>±1.1</td>
<td>174</td>
<td>±3.2</td>
<td>±5</td>
<td>±3.4</td>
<td>±2.0</td>
<td>±0.93</td>
<td>±0.35</td>
</tr>
<tr>
<td>(n = 16)</td>
<td></td>
<td></td>
<td>84</td>
<td></td>
<td></td>
<td>28.6</td>
<td>79</td>
<td>36</td>
<td>95</td>
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<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

*Ht = height; Wt, weight; FEV₁, forced expiratory volume in 1 second; % Pred, percent predicted; SRDB, sleep-related disordered breathing; PaCO₂, partial pressure of arterial oxygen and carbon dioxide while awake; baseline SaO₂, baseline arterial oxygen saturation during sleep; Minim SaO₂, the single lowest SaO₂ value recorded during sleep in each subject; and NS, not significant.

subjects were hospitalized for the duration of their participation in the study. During hospitalization, subjects ate a hospital diet that did not include any alcoholic beverages.

Pulmonary Function Testing

Routine pulmonary function was normal since it was part of the inclusion criteria (Table 1). In addition, hypercapnic and hypoxic ventilatory response studies, upright and supine nasal airway resistance, and maximal inspiratory and expiratory flow-volume curves were performed. All 28 subjects had flow-volume and hypercapnic response studies, 25 had hypoxic studies, and 24 had nasal airway resistance studies.

Hypercapnic and hypoxic ventilatory response studies were performed as previously described. Briefly, the CO₂ rebreathing method with 7 percent CO₂ in 93 percent oxygen was used to measure hypercapnic ventilatory responsiveness, and separately, an isocapnic rebreathing method was used to measure hypoxic ventilatory responsiveness. The end-tidal CO₂ (measured by mass spectrometer) was used as a measure of hypercapnia, and ear oximetry was used to measure hypoxemia by determining arterial oxygen saturation (SaO₂) as percent. Expired ventilation was measured by integration of flow from a pneumotachograph. All variables were recorded on a dynograph recorder. Hypercapnic ventilatory response is reported as the slope (by linear regression analysis) of ventilation versus end-tidal CO₂ in L/min/mm Hg CO₂. Hypoxic ventilatory response also is reported as a slope (L/min%/SaO₂).

Nasal airway resistance was performed by the posterior rhinometry technique. A tight fitting scuba mask which excluded the mouth was used to provide an airtight seal around the nose but still leave the nose unobstructed. A pneumotachograph was tightly fitted to the front of the mask through a hole in the faceplate to measure nasal flow. A large bore tube was placed through the mouth to the back of the pharynx through a sealed mouthpiece to measure pharyngeal pressure. The subject pressed his lips around the mouthpiece to provide an airtight seal (Fig 1). Pressure was measured with a transducer. All signals were recorded on an oscillographic recorder; the flow-pressure data was displayed as X-Y information and photographed for hard copy. The subjects sat upright and were instructed to breathe normally through the nose; inspiratory resistance was measured at 0.45 liters per second and expressed as cm H₂O/L/s (BTPS). Next, the subjects were placed supine (since this approximates the usual sleeping position) on a bed and the measurement was repeated. Typical examples of upright and supine resistance curves are shown in Figure 2. Measurements were obtained in quintuplicate, and the average is reported.

Maximal inspiratory and expiratory flow-volume curves were measured with a wedge spirometer and recorded on the oscillographic recorder. Subjects performed flow-volume curves until three reproducible inspiratory and expiratory curves were obtained. The curves were inspected for "sawtoothing" according to previously published criteria, and in addition, the maximal inspiratory and expiratory flows at 50 percent of vital capacity (MEF 50 percent and MIF 50 percent, respectively) were determined. This latter is reported as the ratio of these flows, namely as the MEF 50%/MIF 50%.

Polysomnography

Polysomnography was performed after all pulmonary function measurements were made. The results of the pulmonary function tests were not known to the polysomnographer. Sleep recordings were carried out at night for at least eight hours on three separate nights. Sleep monitoring consisted of EEGs (two channels), electrooculograms (two channels), and chin EMG using standard techniques. Nocturnal respiratory measurements included ear oximetry (first and third nights), nasal and buccal thermistor signals, and measurement of chest and abdominal movement using a separate strain gauge for each. Using the entire record, sleep stages were...
evaluated according to standard criteria. The results from the first and third nights (ie, nights on which SaO₂ was measured) were similar, and the results reported are from the first night.

An episode of SRDB was defined as a decrease in SaO₂ of at least 4 percent from the immediately preceding baseline. Some of these episodes occurred while airflow continued (ie, nonapneic episodes), and the rest of the episodes occurred with apnea. Apnea was defined as the absence of airflow for 10 s or longer. In general, it can be difficult to separate nonobstructive (ie, central) SRDB from obstructive SRDB without measurement of intrathoracic pressure. An esophageal balloon was not used to measure intrathoracic pressure because of possible adverse effects on other sleep factors. For this reason, all patients with SRDB were grouped together for statistical analyses.

Analysis of Data

The polysomnography data were used to separate subjects into two groups. Although >5 apneas per hour is considered to be significant, there are no similar accepted criteria on number of arterial oxygen desaturations (ie, SRDBs) per hour. However, previous studies have indicated that the number of desaturations per hour is greater than the number of apneas per hour. Also, there was a bimodal distribution of SRDB frequency in this study, with one group of ten subjects having <8 episodes per hour and the remaining 16 subjects having >12 episodes per hour. For these reasons, the ten subjects with less than eight episodes of SRDB per hour of sleep were classified as control subjects. This group had (X ± SEM) 4.3 ± 0.74 episodes per hour and had a minimum SaO₂ during sleep of 88 ± 1.3 percent. The remaining 16 subjects with greater than 12 SRDB episodes per hour of sleep were classified as SRDB subjects. This group had 28.6 ± 3.4 episodes per hour and had a minimum SaO₂ of 79 ± 2.7 percent during sleep (Table 1). Total sleep time was similar in both groups of subjects indicating that differences in exposure to sleep did not account for differences in SRDB. In addition, SRDB episodes were distributed throughout both REM and NREM sleep in all SRDB subjects. It should be noted that the classification of the sleep data was carried out without knowledge of the analyses of the respiratory data. Further specifics of sleep staging will be reported elsewhere, and with respect to sleep, the rest of this report concerns SRDB results only.

The hypercapnic and hypoxic ventilatory responses, the nasal airway resistance, and flow-volume curve results were compared between control and SRDB groups. In addition, based on previous reports, a hypercapnic response of less than 1 L/min/mm Hg and an MEF 50%/MIF 50% greater than 1 were considered to be outside the normal range for purposes of defining prevalence of abnormality. Also, although the hypoxic ventilatory response can vary widely, we considered an essential lack of hypoxic response as defined by an absolute value less than 0.1 L/min/% SaO₂ as abnormal. Elevated nasal airway resistance was interpreted as representing abnormalities (functional or anatomic) of the upper airway from the soft palate to the nose and excluded areas below the soft palate. Elevated MEF 50%/MIF 50% and sawtoothing were interpreted as representing abnormalities of the upper airway excluding the nose. Reduced hypercapnic and hypoxic responses were considered to be abnormalities of chemical control of breathing since results of routine spirometry were normal.

Statistics

The nasal airway resistance data were analyzed by analysis of variance (ANOVA) using both upright and supine data. If the ANOVA was significant, unpaired t-tests were used to determine which differences accounted for the significance. Since only a direct comparison between control and SRDB subjects was possible for each of hypercapnic, hypoxic, and flow-volume curve results, the unpaired t-test was used to determine if differences were present with these measurements. A p value of less than 0.05 was significant.

RESULTS

Subject Data

Age, height, weight, FEV₁, awake PaO₂ and PaCO₂, and baseline SaO₂ during sleep were similar between SRDB and control groups (Table I). This indicated that these variables did not markedly affect the prevalence of SRDB between these two groups.

Respiratory Abnormalities

Thirteen subjects had 14 respiratory abnormalities. The one subject with two abnormalities had a decreased hypoxic as well as a decreased hypercapnic ventilatory response and had an average degree of SRDB (29 SRDB episodes per hour of sleep with a minimum SaO₂ of 84 percent). Specifically, the group as well as individual abnormalities were as follows:

1. Hypercapnic Ventilatory Response: The hypercapnic values were significantly less in the SRDB group compared to the control group (Table 2). In addition, four of 16 SRDB subjects and none of the ten control subjects had a value less than 1 L/min/mm Hg (Fig 3). The waking PaCO₂ in these four SRDB subjects was 54, 36, 39, and 41. That is, none of these subjects was hypercapnic.

2. Hypoxic Ventilatory Response: The hypoxic re-
Table 2—Awake Respiratory Function* |

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Nasal Airway Resistance Upright (CM H₂O/L/sec)</th>
<th>Nasal Airway Resistance Supine (CM H₂O/L/sec)</th>
<th>Hypercapnic Response (L/min/MM Hg Pco₂)</th>
<th>Hypercapnic Response (L/min/% SaO₂)</th>
<th>Hypoxic Response (L/min/% SaO₂)</th>
<th>Sawtoothing (Prevalence)</th>
<th>MEF 50%/MIF 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.50</td>
<td>2.40</td>
<td>3.58</td>
<td>-0.84</td>
<td>3/10</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>N = 10</td>
<td>±0.46</td>
<td>±0.32</td>
<td>±0.62</td>
<td>±0.39</td>
<td>6/16</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>SRDB</td>
<td>2.42</td>
<td>3.60</td>
<td>1.92</td>
<td>-0.50</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 16</td>
<td>±0.41</td>
<td>±0.43</td>
<td>±0.20</td>
<td>±0.092</td>
<td>±0.055</td>
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<td></td>
</tr>
<tr>
<td>Significance Level</td>
<td>NS</td>
<td>p&lt;0.05</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*MEF 50% and MIF 50% is maximal expiratory and inspiratory flow at 50 percent of vital capacity; for other abbreviations, see footnote to Table 1.

response did not differ significantly between control and SRDB subjects (Table 2). However, none of the ten controls but three of 15 SRDB subjects had absolute values of less than 0.1 L/min/% SaO₂. The waking PaO₂ in these three SRDB subjects was 68, 88, and 89. That is, only one of these three subjects was even mildly hypoxic. The range of actual values in the control group was from -0.22 to -4.30 L/min/% SaO₂ and in the SRDB group was from +0.07 to -1.21.

(3) Nasal Airway Resistance: Upright nasal airway resistance did not differ significantly between control and SRDB groups (Table 2). Upright values are similar to those reported by others. Supine nasal airway resistance did not change (compared to upright) in the control group but did rise significantly in the SRDB group (Table 2). Based on the mean and standard deviation of the control supine nasal airway resistance results, we considered all supine values greater than 4 cm H₂O/L/sec to be elevated (ie, >1.6 times the standard deviation plus the mean). Four of 14 SRDB subjects and one of ten control subjects had such elevated values (Fig 3).

(4) Flow-Volume Curves: Sawtoothing did not differ in prevalence between groups (Table 2). The MEF 50%/MIF 50% ratios did not differ between groups (Table 2). However, none of the ten controls and two of the 16 SRDB subjects had a ratio greater than 1 (1.1 in each case).

Correlation of SRDB to Awake Respiratory Abnormalities

The degree of desaturation and number of SRDB episodes correlated significantly with supine nasal airway resistance and hypercapnic ventilatory response, respectively. Specifically, the number of SRDB episodes per hour of sleep correlated with supine nasal resistance (r = 0.43, p<0.05), and the hypercapnic response correlated with the minimum SaO₂ during sleep (r = 0.42, p<0.05). Of note, the hypoxic ventilatory response, the MEF 50%/MIF 50%, and subject weight did not correlate significantly with either the number of desaturations per hour or the minimum SaO₂ during sleep.

Discussion

Our results indicate that asymptomatic, older male subjects with SRDB who are otherwise healthy can have, while awake, diminished chemical control of breathing and narrowing of the upper airway compared
to a matched group without SRDB. Our results also demonstrate a high prevalence of SRDB in this subject population.

Our study is the first to examine chemical control of breathing in awake, asymptomatic, healthy, older men with SRDB. Our results indicate that hypercapnic ventilatory responsiveness while awake is diminished in some subjects with SRDB. In addition, three SRDB subjects had essentially no hypoxic ventilatory response. These results suggest that diminished chemical control of breathing is (1) more prevalent in the SRDB subjects, and (2) is not associated with abnormalities of awake arterial blood gases since the PaO₂ as well as the PaCO₂ were similar in control subjects and in SRDB subjects with diminished hypercapnic and hypoxic ventilatory responses. This is in contrast to patients with symptomatic sleep-apnea syndrome in whom diminished awake hypercapnic and hypoxic ventilatory responsiveness is usually not found unless daytime hypercapnia and hypoxemia is present.12 The reason for this difference between asymptomatic SRDB subjects and symptomatic sleep-apnea syndrome patients is not defined; a possible hypothesis is that asymptomatic SRDB subjects with diminished chemical control of breathing may develop daytime hypercapnia and hypoxemia should they present with the full-blown sleep-apnea syndrome.12 On the other hand, it is possible that this difference indicates that asymptomatic SRDB and the symptomatic sleep-apnea syndrome are fundamentally different conditions.

Our study is the first to examine the patency of the upper airway in awake, asymptomatic, healthy older men with SRDB. Our results indicate that supine nasal airway resistance is elevated in some subjects with SRDB. Since the upright values did not demonstrate such a relationship, it is likely that the elevated supine resistance was, at least partly, the result of a repositioning of the soft and possibly congested tissues of the nasopharynx (ie, a "functional" rather than a fixed anatomic obstruction).10 In addition, two of the SRDB subjects had an MEF 50%/MIF 50% greater than one; such a value is suggestive of variable extrathoracic obstruction in these subjects.9

In general, our results indicating awake narrowing of the upper airway in asymptomatic SRDB subjects are consistent with studies in awake symptomatic patients with either the sleep-apnea syndrome or SRDB. Elevated pulse-flow resistance, elevated nasal airway resistance, and a decrease in upper airway size as measured by computerized tomography in patients with the obstructive sleep-apnea syndrome,10,11,24 and an increase in the MEF 50%/MIF 50% ratio in symptomatic patients with sleep-disordered breathing9 have been reported. Furthermore, it has been long recognized that obstructive pathology of the upper airway such as micrognathia can be associated with the sleep-apnea syndrome.7 "Saw-toothing" on the flow-volume curve also has been reported to be more prevalent in sleep-apnea syndrome patients.8 However, we were unable to demonstrate an increased prevalence in our SRDB subjects. The reasons for this discrepancy are not defined, but in any case, do not substantially affect our conclusions.

There was a correlation between supine nasal airway resistance and severity of SRDB as indicated by number of SRDB episodes per hour. Possible hypotheses to explain this correlation include the following: (1) preexisting narrowing of the nose and nasopharynx is worsened by hypotonia of the pharyngeal muscles during sleep; (2) the possible presence of receptors in the upper airway has been postulated to contribute to sleep-apnea,25 it can be speculated that preexisting upper airway obstruction might interact with such receptors to produce central or obstructive SRDB; and (3) upper airway obstruction and SRDB may be processes that independently derive from aging and do not necessarily contribute to each other. For example, anatomic abnormalities of the nose such as a thickened nasal mucosa might hypothetically increase in prevalence with age simply because of the greater opportunity for such to occur with the passage of time. Further study is needed to resolve these questions.

There was a correlation between awake hypercapnic ventilatory response and minimum arterial oxygen saturation during sleep. Additionally, although the hypoxic response was not correlated with minimum saturation during sleep, it should be reemphasized that three SRDB subjects had essentially no awake hypoxic response. Since the tone of the upper airway muscles may be regulated, in part, by chemical stimulation of the respiratory center,26,27 diminished chemical control of breathing can be hypothesized to contribute to collapse of the upper airway muscles and consequent obstructed breathing during sleep in some of our SRDB subjects. Furthermore, diminished chemical control of breathing may hypothetically exaggerate central episodes of SRDB, and in addition, may indicate a diminished arousal response to hypercapnia and hypoxemia;28 this latter may lead to prolonged episodes of both obstructive and central SRDB and, thereby contribute in this study to the degree of arterial oxygen desaturation during sleep. On the other hand, diminished hypercapnic and hypoxic ventilatory responses have been reported to occur in elderly persons29,30 and have not been correlated with the presence of the sleep-apnea syndrome in subjects of varying ages;31 these findings suggest the possibility that the diminished ventilatory responses in our subjects may have been an independent result of aging and did not necessarily contribute to SRDB. Nevertheless, the mean hypercapnic and hypoxic response values in
our subjects did not differ markedly from values reported for younger people. Further study is needed to clarify the role of diminished chemical control of breathing in subjects with SRDB.

Obesity has been previously reported to contribute to SRDB. However, our present results indicate no correlation of SRDB with weight in a group of predominantly nonobese patients. This suggests that obesity is not essential for the production of a high prevalence of SRDB.

Our study examined the prevalence of SRDB in asymptomatic, healthy, older male subjects. Because of methodologic differences between our study and those of others, including screening criteria and varying definitions of SRDB, our results cannot be directly compared to other studies of essentially healthy older men. However, despite the methodologic differences, prevalence rates were high in all studies including our own and varied from 44 percent to 82 percent of subjects over the age of 45. Furthermore, in two of the studies, 19 younger subjects were also investigated and none of these 19 subjects had a significant degree of either sleep-apnea or SRDB. The precise reasons why sleep-apnea and SRDB are increased with age even in otherwise healthy men is not fully defined by our study. However, our results do suggest the hypothesis that obstruction of the upper airway as well as diminished chemical control of breathing may contribute to SRDB, perhaps as a result of the aging process.

Aging is associated with a number of signs and symptoms including dementia, impotence, and systemic hypertension with its consequent vascular complications. These findings can also occur with the sleep-apnea syndrome and can be reversed by therapy of the syndrome. By analogy with the sleep-apnea syndrome, the possibility that SRDB in older persons might contribute to dementia, etc., is an attractive, and as yet, unproven hypothesis. Should this hypothesis be proven, then therapy of SRDB, possibly through therapy of awake respiratory abnormalities, may be useful in ameliorating some signs and symptoms that are associated with aging. It should be noted that by design, the subjects in the present study did not have obvious age-related illnesses apart from systemic hypertension. For this reason, the possibility that SRDB is essentially benign must be considered as an alternative hypothesis to the possibility that SRDB is the forerunner of serious illness.

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**International Congress on Echocardiography**

The International Congress on Echocardiography (with concurrent session on Mechanocardiography), organized by the Indian Society of Medical Ultrasound and Indian Society of Mechanocardiography, will be held December 9-11 at the Hotel Taj Intercontinental, Bombay, India. For information, contact: Dr. C. V. Vanjani, Secretary General, 505 Doctor House, G. Deshmukh Marg, Bombay 400 026, India.