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Chronic glandular bronchitis in young individuals residing in a metropolitan area

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Abstract A study of 161 Los Angeles County residents aged 12–28 years old who had died sudden violent deaths showed frequent and severe chronic glandular bronchitis (CGB), that is to say grade ≥5 (0–10) chronic inflammation involving at least one, half or more, and all submucosal glands in 53.4%, 21%, and 4.4% of the main stem bronchi, respectively. The mean plasma cell/gland/bronchus was high (≥5) for 22 subjects (13.7%), while only 2 bronchi (1.2%) had a correspondingly high lymphocyte mean (P<0.001). Of the bronchi, 75.2% were affected by glandular atrophy (≥5 in 8.1%), 10.6% had neutrophil infiltration of glands, and 3.1% had acute sialadenitis. Of the total of 1040 glands, CGB was found in 83.8% (≥5 in 26.5%). Of 25 non-smokers identified, 14 (56%) had some degree of CGB in ≥50% of the glands, severe in 7 (26%). Severe CGB in many young individuals raises concern that a subpopulation of living cohorts may have an increased susceptibility to disease and a rising incidence of chronic lung disease. Demographic analysis is pending, but respiratory infection, smoking, adverse socioeconomic factors, and air pollution are all potential causative factors. Since pollution in Los Angeles frequently exceeds air quality standards, an ongoing multicity study is attempting to distinguish between the suspected effects of air pollution and confounding variables.

Key words Bronchus gland · Inflammation · Fibrosis · Atrophy

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Introduction

In an earlier study of 107 Los Angeles County residents 14–25 years of age whose deaths were sudden and violent, severe inflammation of the centriacinar region (CAR) was found in 27% of the lungs [44]. A subsequent study of main stem bronchi from the same group, with an additional 33 cases, showed that 32% had severe chronic inflammation of the epithelia lining and lamina propria, a lesion we designated chronic mucosal bronchitis (CMB) [45]. The present study, with the group now expanded to 161 individuals, reports on inflammation of submucosal glands, i.e., chronic glandular bronchitis (CGB). There is surprisingly little information available on inflammation and other alterations of submucosal glands, and there has been no prior report of a high indicence of CGB in young individuals dying sudden violent deaths. The present paucity of information reflects a significant underappreciation of central airway inflammation as a potentially serious adverse health effect. It is the purpose of the present study to document the frequency, severity, and nature of injury to submucosal glands in main stem bronchi of young individuals who ordinarily would be considered part of a "well" population.

Methods

The details of procedures for processing lungs that were obtained from the Los Angeles County Medical Examiner-Coroner's Office have been reported earlier [44]. In brief, the lungs were obtained

from autopsies of youths who died suddenly from homicide or vehicular accidents. Eligibility criteria were sudden death, residency in Los Angeles County, age 15–25 years, no historical record or signs at autopsy of drug use, no evidence of disease on the basis of the routine postmortem examination, and autopsy less than 3 days after death. The main stem bronchus of each left lung (or right lung when the left was not available) was cannulated with a loose-fitting plastic tube and secured at the bronchial margin with an 18-G hypodermic needle inserted into a cork. The lung was immersed in a 90 l tank of 10% of phosphate-buffered formalin and fixed by perfusion-inflation at 25 cm H_2O for 72 h or more. After fixation, a complete ring of the main stem bronchus was excised at a point ~2 mm from the segmental division. Paraffin block sections were stained with haematoxylin and eosin (H&E), periodic acid–Schiff, and Alcian blue.

A single 4-μm-thick H&E-stained section of the left or right main stem bronchus was used for quantitation. Specimens were analysed without identification or access to demographic data. Sections in which glandular preservation was poor and any that were otherwise technically unsuitable were excluded from the analysis. All submucosal glands in the bronchial ring section were classified by size under 30× magnification (2.5× objective). Small glands were defined as under 50% of the 5.4 mm diameter of the microscopic field, medium glands as 50% or more of, but less than the field diameter, and large glands as 100% or more, but less than an estimated 125%, of the field diameter. Glands larger than 125% of a field diameter were arbitrarily divided into two or more units of approximately equal size for independent readings. Very small glands were measured by combining them as an arbitrarily defined single glandular aggregate. The measurement of leucocytic infiltration was limited to glandular areas and was graded on a scale of 0–10 under a magnification of 200× (16× objective).

Lymphocytes, plasma cells, and other leucocytes in the glandular infiltrates were identified by their morphological characteristics. A single lymphocyte or plasma cell in a gland, or none at all, was classed as grade 0. Grade 1 ranged from as few as two lymphocytes or plasma cells to scattered cells involving less than 5% of the gland. Grade 2 infiltration ranged from 5% to less than 25% of the gland. Infiltration involving approximately one-third of the gland was recorded as grade 3, and an estimated 40% involvement as grade 4, with grades 5–9 corresponding to percentage infiltration in increments of 10%. Essentially complete leucocytic effacement of the gland was classed as grade 10. The presence of lymphocytic infiltrates around intraglandular vessels ("perivascular cuffing") added a subjective weighting to the grade. Lymphoid nodules within glands were recorded, but were not a part of grading.

Glandular atrophy was graded on a scale of 0–10 to approximate the percentage of acinic loss within each gland. A grade 10 was defined as atrophy just short of complete replacement, which means a remnant of glandular tissue served to identify a glandular site. Dilatation of ducts was judged on the basis of a generalized or bulbous distension, with or without mucus inspissation and/or flattening of lining cells. A grade 6 was arbitrarily assigned to the maximal dilatation observed after screening of the bronchial sections, namely 0.575 mm. We also noted a report by Duprez and Mampuys [16], based on alcohol-fixed bronchi, that described "dilated ducts from the glands" as large as 1.2 mm. A subjective grading was also applied to the dilatation of acinic structures. Serous and mucous cells in each gland were evaluated according to percentage composition. Other alterations recorded included the presence of oncocytes [36], mucus inspissation in ducts and glands, angiectasia, and sialadenitis (acute exudative and chronic). "Sialadenitis" is used as the bronchial gland counterpart of leucocytic infiltration of ductal walls and/or lumina of salivary glands.

Statistical analysis was based on Student's *t*-test, with significance at a 95 percentile level (2-tail).

Demographic data, derived from next-of-kin interviews and records of the Los Angeles County Department of Coroner, were acquired independently of this study (to control for bias) and will be reported separately. Also to be reported separately are the results from an ongoing image analysis quantitation of submucosal glands, which will provide objective data on atrophy and also on measurements of mucous, serous, and antibody-secreting cells.

Results

Of 175 lungs accessioned, the bronchi of 161 were technically suitable for study. Of the 161 subjects, 140 were male and 21 were female. Ages based on confirmed data ranged from 12 to 28, with a mean age of 20 years. The average number of glands, and glandular aggregates (see Methods) in the 161 bronchial sections was 6.5, with a range of 2–18. All but 4 of the bronchi (97.5%) had at least one submucosal gland with some lymphocytic and/or plasmacytic infiltration. In 81.9% of bronchi, the infiltrates were comprised of both lymphocytes and plasma cells. Lymphocytes in bronchial glands tended to be slightly more pervasive than plasma cells, being present in 95.7% of the glands, while plasma cells were present in 87.6%. Glandular infiltrates were exclusively lymphocytic or plasmacytic in a small percentage of the bronchi (8.7% and 2.5%, respectively). In 91 bronchi (56.5%), all submucosal glands had a lymphocytic and/or plasmacytic infiltrate.

Severe lymphocytic and/or plasmacytic infiltration (≥5) was recorded for at least one gland in 86 bronchi (53.4%), in half or more of the glands in 34 bronchi (21.1%), and in every gland in 7 bronchi (4.4%). The mean leucocyte/gland/bronchus was 2.3 for plasma cells and 1.95 for lymphocytes, a plasma cell predominance of borderline significance (P=0.07). Upper quartile analysis of the means showed a highly significant predominance of plasma cells in glandular infiltrates, as reflected by 22 bronchi (13.7%) with a ≥5 plasma cell/gland/bronchus mean vs only 2 bronchi (1.2%) with the ≥2 corresponding lymphocyte mean (P<0.001).

Of the 1040 submucosal glands in 161 bronchi, lymphocytic and/or plasmacytic infiltration was present in 83.8% (Figs. 1, 2), and at a severe level (≥5) including perineural inflammation in 26.5% (Figs. 3–6). As was the case for measurements per bronchus, lymphocytic infiltration per gland was slightly more pervasive than was plasma cell infiltration: 73.9% vs 64.7% of the glands, respectively. However, there were twice as many glands with severe plasmacytic infiltration (≥5) as with severe lymphocytic infiltration: 21.3% of the glands vs 10.1%, respectively (P<0.001), and also a greater plasmacytic than lymphocytic mean: i.e., 2.44 vs 1.95, respectively (P<0.001). Effacement of large portions of glandular tissue by combined lymphocytic and plasmacytic infiltrates (Figs. 4, 6) was noted, and in one instance this resembled a lymphoepithelial lesion at low magnification but was found on close examination to be largely a plasma cell infiltrate (Fig. 7). There were a number of instances of periductal leucocytic infiltration (Figs. 3, 4), and also several bronchi with ganglia and/or nerve bundles surrounded by dense leucocytic infiltrates (Fig. 5), including those of nonsmokers.

Neutrophilic infiltration of glandular interstices occurred in 17 bronchi (10.6%), but was generally slight (≤grade 2). In 5 of the 161 bronchi (3.1%) neutrophilic infiltration of glands, ductal lamina and/or ductal walls were accompanied by prominent aggregates of neutro-

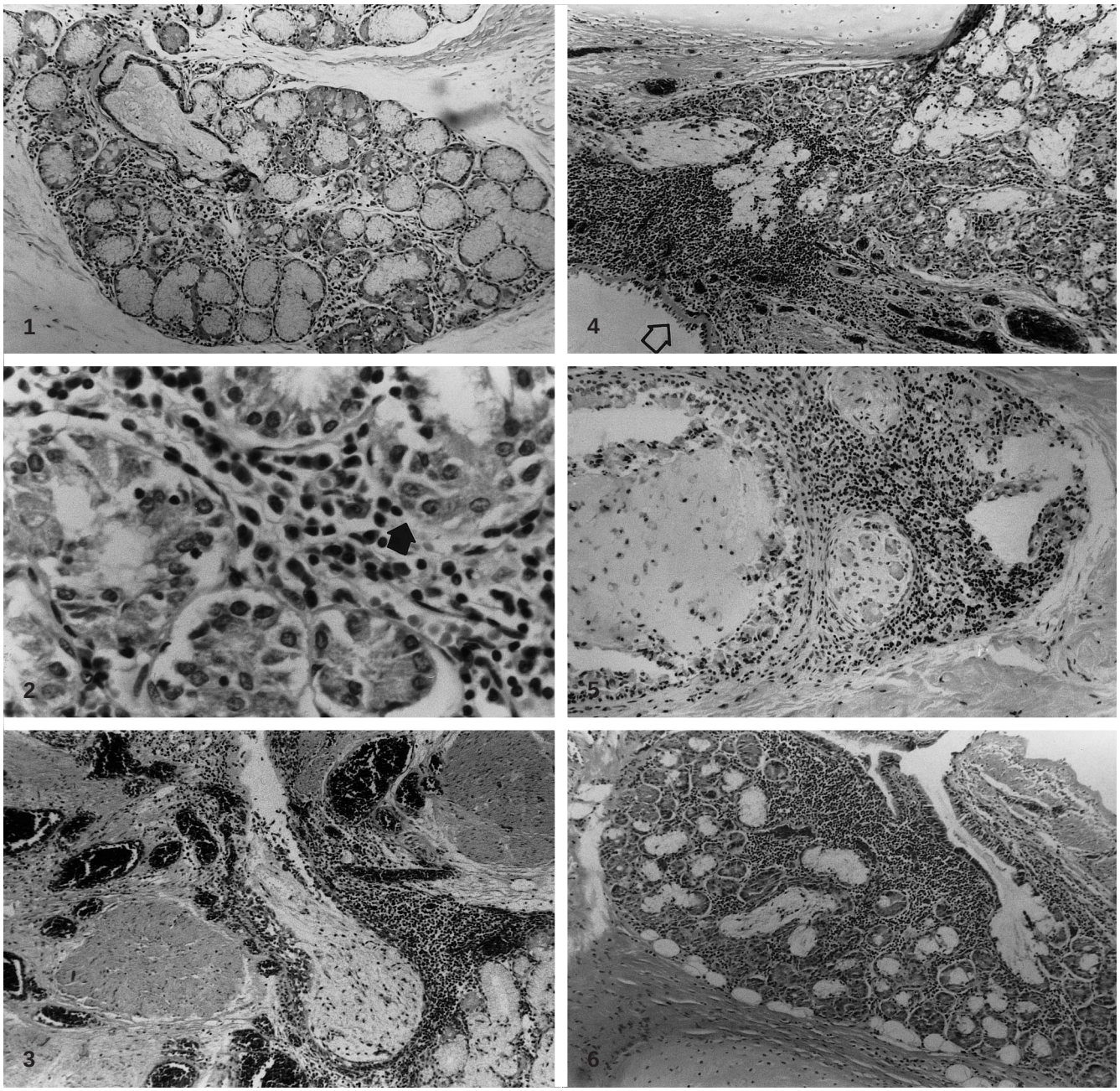

Fig. 1 Marked leucocytic infiltration of submucosal gland (grade 6). There are ~500 leucocytes, predominantly plasma cells, in the glandular interstices (hand count and image analysis quantitation). The central duct is slightly dilated (147 µm maximum width). Decedent is a 22-year-old Caucasian male. H&E, ×84

Fig. 2 Marked plasma cell infiltration. The interstitium has abundant plasma cells and lymphocytes. Focal acinic atrophy (*arrow*) is evident from partial loss of basement membrane, architectural disarray, and poor cellular definition. Decedent was a 16-year-old black male. H&E, ×530

Fig. 3 Periductal lymphocytic infiltration (nonsmoker). A marked lymphocytic infiltrate surrounds a duct with a bulbous dilatation (290 µm). A dense, mainly lymphocytic infiltrate extends into much of the glandular tissue. Angiectasia is marked. Decedent was a 21-year-old Caucasian male. H&E, ×84

Fig. 4 Marked lymphocytic infiltration. Lymphocytes largely replace the adluminal portion of the gland. Dilated ductules and acini are prominent and an 11-µm-thick basement membrane is present (*arrow*). Angiectasia is also prominent. Decedent was a 25-year-old Hispanic male. H&E, ×84

Fig. 5 Perineural and periganglionic infiltration. A ganglion (*bottom centre*) and nerve bundle (*top centre*) are surrounded by a dense, mainly lymphocytic infiltrate. The adjacent gland (*bottom right*) has been largely replaced by leucocytes. Decedent was a 23-year-old Caucasian (Hispanic) female. H&E, ×133

Fig. 6 Severe leucocytic infiltration (grade 8) in a nonsmoker. A dense infiltrate, mainly plasma cells, replaces and/or obscures portions of the gland. Ductal dilatation is slight to moderate. Decedent was a 17-year-old black male. H&E ×33

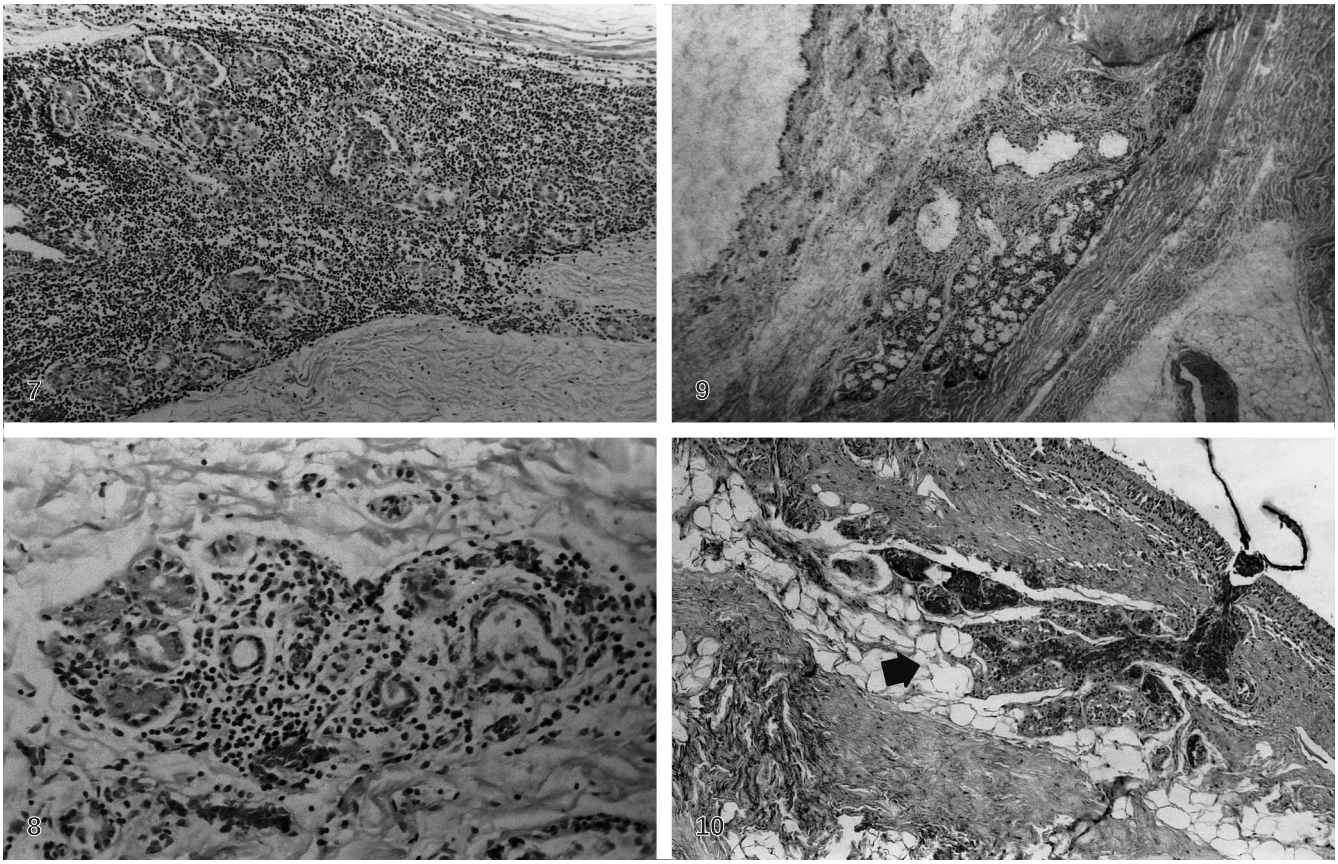

Fig. 7 Marked inflammation (grade 9). Same case as Fig. 2. The gland is almost totally effaced by a leucocytic infiltration that is predominantly plasmacytic. Decedent was a 16-year-old black male. H&E, ×84

Fig. 8 Marked glandular atrophy. Most of the glandular tissue has been lost, leaving behind a loose stromal tissue containing numerous lymphocytes and plasma cells. Decedent was a 25-year-old black male. H&E, ×209

Fig. 9 Marked glandular atrophy with fibrosis. Approximately half of the gland is atrophic and replaced by moderately dense connective tissue. There is moderate ductal dilatation and a slight to moderate leucocytic infiltration. Decedent was a 20-year-old Caucasian male. H&E, ×33

Fig. 10 Marked atrophy with fat replacement. The boundary of the gland is imprecisely defined (*arrow* points to truncated margin at junction with fat), but at least one-half of the gland is replaced by fat. Note string-like excrescences of inspissated mucus. Decedent was a 25-year-old Hispanic female. Alcian Blue, ×84

phils (acute exudative sialadenitis). In 1 bronchus, all 5 glands showed acute sialadenitis, and 1 of the ducts showed focal ulceration of the epithelial lining. Chronic inflammation of glandular ducts (chronic sialadenitis) was evident in 11 glands of 8 bronchi. Some degree of glandular infiltration by eosinophils occurred in 19% of the bronchi. Details of the data on eosinophilic infiltration of the glands and related bronchial wall alterations will be reported separately.

Glandular atrophy ranged from suble loss of basement membranes of acinic cells (Fig. 2) to a disappearance of acini (Fig. 8), and included partial replacement by fibrous (Fig. 9) and fatty (Fig. 10) tissues. Some degree of glandular atrophy was present in 75% of the bronchi, and the atrophy was marked in 8.1%. Ductal (Figs. 3, 4, 6) and/or acinic dilatation (Fig. 4) was present to some degree in 73.3% and 52.2% of the bronchi, respectively. Severe ductal dilatation (≥5) occurred in 9 bronchi (5.6%) and severe acinic dilatation (grade 6) in glands of just 1 bronchus. The maximal ductal dilatation observed was 575 μm in diameter and, as indicated in the Methods section, it was arbitrarily assigned a grade 6. Duct ectasia, dilatation of a duct with protrusion through the muscle wall [13], was not found. There was a single instance of atypical epithelial hyperplasia of a duct. The serous proportion of the submucosal glands varied from 27% to 95%, with a mean value of 56.5%.

From one to five nodular aggegates of lymphoreticular tissue with rare germinal centres were found within submucosal glands in 104 bronchi (64.6%). Occasionally, a portion of the ductal lining was incorporated within a lymphoreticular nodule and resembled von Hayek's "lymphoepithelial organ" or "lympho-epithelium" [7]. An isolated finding was the presence of Warthin-Finkeldey cells in a lymphoid nodule in association with a heavy eosinophilic infiltrate. As noted earlier, the presence of nodular aggregates was not influential in the grading of glandular inflammation, but perivascular lymphocytic cuffing within a gland, which occurred in 12 bronchi (7.5%), was a weighting factor. Angiectasia in the proximity of glands

and in association with inflammatory infiltrates was fairly common, and exceptionally prominent in several bronchi (Figs. 3, 4). Oncocytes, ordinarily associated with older age groups [36], were found in bronchial glands of 5 of the youths, including a 16-year-old.

At the time of this report, the co-author responsible for analysis of the demographic data (R.B.E.) had obtained smoking histories from 44 subjects and identified 25 nonsmokers. After our pathological study had been completed, the smoking status of the 44 subjects for whom smoking histories had been elicited was released to us. Of the 25 non-smokers, 14 (56%) had chronic inflammation involving half or more of their bronchial glands and in 7 (28%) at least one gland was affected by severe (≥5) inflammation (Fig. 6). For the nonsmokers, the mean of plasma cells/gland/bronchus was 3.7, as opposed to 2.9 for the lymphocyte mean (NS). An upper quartile analysis was highly significant ($P<0.006$), reflecting in large part the finding of 6 nonsmokers with a plasma cell/gland/bronchus mean at a severe level (≥5) as opposed to just one nonsmoker with a mean of 5 for lymphocytes. A correlation of the present findings with demographic data (that includes cotinine and cannabinoid assays of blood, tissues, and/or hair from some of the subjects) is in progress as an independent study.

Discussion

The magnitude of CGB observed is not only remarkable for 12- to 28-year-old individuals (mean age of 20) who died suddenly from violence but would be unusual even for symptomatic chronic bronchitics. In the latter respect, a 1973 report by Thurlbeck [49] stated that "Inflammatory changes are present in the bronchi but are surprisingly slight and cannot be used as a diagnostic criterion for chronic bronchitis." Moreover, a "legitimate objection" had been raised in 1984 to the use of the term "chronic bronchitis," since there was "usually no evidence (of inflammation) in the hypertrophied glands" or bronchial walls [18]. Only isolated opinions attributing clinical significance to bronchial inflammation had been expressed [2] prior to 1985, but the report that year by Mullen et al. [37] provided, as recently stated by Thurlbeck [50], "convincing evidence of inflammation in chronic bronchitis." More specifically, Mullen et al. [37] noted that lung cancer patients with symptomatic chronic bronchitis had greater mucosal, glandular, and glandular duct inflammation than those without symptoms. A strict comparison of their findings with ours is precluded by a number of factors. In particular, the presence of bronchial carcinoma in most of the lungs would be expected to cause some secondary inflammation. Also, the mean age of their subjects was 60 and histopathological details were not provided. Data from other reports on bronchial gland inflammation also give relatively limited pathological data. One of two reports is that of Gaillard et al. [20], who examined biopsy tissues from 30 children with recurrent bronchitis and noted dense lymphocytic infiltrates in the submucosa but "rarely around the deepest glands." The second report, by Soutar et al. [46, 47], deals with the examination of entire rings of main stem bronchial tissue and describes "large and numerous" IgA-containing cells in glands of "incidental" bronchitics. Several reports on bronchial inflammation may include glandular involvement, but do not state so specifically. Gong et al. [24] examined bronchial tissues from subjects who had volunteered for biopsy studies and found that three of four nonsmokers had "mild to moderate submucosal inflammation with numerous plasma cells and polymorphonuclear leukocytes." Their data are of special interest, since the subjects in the study had resided in Los Angeles County and the submucosal tissues contained neutrophils as well as plasma cells. Salvato [42] observed a "heavy lymphocytic and round cell infiltration" in bronchial tissue from 24 "healthy controls" who had volunteered for biopsy. The heavy infiltration was not specifically quantitated, but the report states that the exudates did not distinguish between control, bronchitic, and asthmatic individuals. A report by Foresi et al. [19] on submucosal inflammation in 13 asthmatics and 6 "healthy subjects" also found that "a large overlap exists with that in healthy individuals."

A new observation from the present study is the demonstration of a significantly greater number of plasma cells than lymphocytes in glands with severe (≥5) levels of inflammation ($P<0.001$). The plasma cell dominance in glands contrasts with our earlier finding of lymphocytic dominance of leukocytic infiltrates of the mucosa: we found 28.6% of bronchi with severe lymphocytic infiltration of the mucosa, as opposed to only 3.6% of bronchi with severe plasma cell infiltration [45]. The plasma cell distribution appears to be the reverse of the gradient reported for lymphocytes, namely progessively diminishing numbers of lymphocytes from the mucosa towards the submucosal tissues [30, 39]. The presence of lymphocytes is not necessarily abnormal. Lymphocytes appear in the human bronchial submucosa 1 week after birth and in the human lung at 16 weeks of gestation [29]. They are also commonly seen at the termination of mucosal glands [17] and are consistently found in lavage fluid and bronchial biopsy tissue from individuals for all ages who have no apparent respiratory disease [19, 32]. We found "amoeboid and migratory" forms of lymphocytes to be virtually ubquitous in tissue cultures of both mucosal lining cells and submucosal glands [43]. These dynamic and migratory forms may reflect a "surveillance" activity that is not necessarily a response to injury. They appear to be counterparts to the "irregular" lymphocytes in the mucosal lining that Jeffery observed, a dynamic activity "frozen" by glutaraldehyde fixation [30]. Neutrophilic infiltration of glands was relatively infrequent and slight (10.6% of the bronchi), as was focal acute inflammation of bronchial gland ducts (3.1% of bronchi), the latter defined as an "acute exudative sialadenitis". The isolated and focal nature of inflammation at both sites suggests that the incidence would be higher with greater sampling. Drainage of neutrophils into the bronchial lumen from an

acute exudative sialadenitis may in part explain the seemingly paradoxical circumstance of neutrophils within lavage fluid when they are not observed in tissue sections of the airway or lung parenchyma. Lymphoreticular nodules were excluded from the grading of glandular inflammation in view of their present controversial relationship to respiratory disease [38].

Glandular atrophy has surprisingly little attention, being mentioned briefly as a part of chronic bronchitis in a 1965 report by Wright and Stuart [52]. The present finding of severe atrophy involving at least one gland in 8.1% of bronchi (Figs. 8–10) is most probably understated. Large volume quantitation is essential for evaluating subtle acinar atrophy and the magnitude of fatty and/or fibrous replacement but, as Whimster et al. [51] have emphasized, this is an exceptionally formidable challenge. Near-total fibrous replacement of a gland suggests a mechanism to explain in part the subepithelial fibrosis of bronchi seen in asthmatics [4]. The ductal dilatation we observed may be comparable to the "tantalum trapping" seen in asymptomatic individuals volunteering for bronchographic examination [21], but it seems less marked than the cystic dilatation of glandular ducts found in bronchitics [16]. The absence of a diverticulosis-like "ductectasia" [13] probably reflects the young age of the subjects in this study. String-like mucus emerging from dilated glandular ducts (Fig. 10) adds support to a recent study [3] suggesting that Curschmann's spirals may originate within ducts as well as within small bronchi and bronchioles. The mean serous cell/mucous cell ratio of 56% compares to the approximately 60% reported as normal for healthy individuals [5]. However, the wide range we observed (27–95%) warrants further study, bearing in mind that a transformation of serous cells to mucous cells has been reported in chronic bronchitics [23]. Another point warranting further study is the marked angiectasia present in some glands (Figs. 3, 4), notwithstanding the present controversy about its clinical significance and role in airflow obstruction [11, 12]. Perineural inflammation (Fig. 5) appears to be a largely overlooked lesion, mentioned only briefly in one report as a part of chronic bronchitis [37]. The suggestive Warthin-Finkeldey giant cells found in one of the bronchial lymphoid nodules is an isolated finding that does not necessarily implicate a rubeola infection [8, 31].

The causation is undoubtedly multifactorial, with major roles played by respiratory infection and what has been referred to as "childhood respiratory trouble" [9, 22]. Also highly suspect is tobacco and/or marijuana smoking [24], passive as well as active, but with several reservations. Severe CGB was found in 7 of 25 nonsmokers, and teenagers would tend to have relatively low pack-years of smoking. In addition, chronic bronchitis is well known to occur in adult nonsmokers [34]. Ambient levels of air pollution have also been implicated as a cause of lung injury [1, 6, 33]. A report by Thurlbeck [48] points out, that "in the United Kingdom air pollution may frequently cause bronchitis in the absence of heavy smoking." It is certainly relevant that all subjects in this study resided in Los Angeles County, where Federal air quality standards, and that for ozone in particular, are frequently exceeded. In the latter respect, experimental studies exposing animals [14, 26] and humans [4] to ambient levels of ozone have produced inflammation of the nose and airways, and nasal alterations have been found in Mexico City residents exposed to air pollution with especially high ambient levels of ozone [10]. Adverse socioeconomic factors can predispose to respiratory illness [35, 40], and preliminary demographic information indicates that the majority of the subjects in this study were minority groups from economically disadvantaged areas. Data on occupational and hobby-related exposures are part of an independent study, but neither of these types of exposure would be expected to be frequent or major factors in lung injury of young subjects. A final consideration is that known drug users were excluded from the study by historical and autopsy data.

As Hoidal has aptly stated, the consequences of central airway inflammation are "poorly understood and under-investigated" [28], which is in contrast to the well-recognized effects of peripheral airway disease on airflow obstruction [27]. Speculatively, it seems likely that the host defence system of central airways would be impaired by CGB and thus contribute indirectly to peripheral airway disease. Recently, central airway inflammation has been implicated in functional alteration by data showing a direct relationship between abnormal air flow in the chronic bronchitis and infiltration of the subcarinal bronchial mucosa by T-lymphoctes and macrophages [15]. Also, it has been suggested that bronchial inflammation may be ameliorated by steroids [25]. From the foregoing considerations, there is reason to be concerned that living cohorts of these young individuals are at risk for increased susceptibility to disease in general, and for an increase in chronic lung disease over the long term. In the latter respect, a study by Mann et al. [35] has found that the best predictors of adult lower respiratory illness are childhood lower respiratory illness, parental bronchitis, home environment in general, later smoking, and atmospheric pollution. In view of the frequent exceedences of air quality standards in Los Angeles County, and the likelihood that lung inflammation related to air pollution contributes significantly to an acceleration in the rate of lung decline, multicity study of the lungs of young individuals is ongoing, in which an attempt is being made to distinguish the adverse effects of ozone and other air pollutants from diverse confounding variables.

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