Ozone – 42 years later

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My invitation to give this lecture at a continuing medical education course at St Paul's Hospital, Vancouver, British Columbia, on January 21, 2006, which the present article summarizes, included the suggestion that I should select some topic that I had been interested in for most of my professional life, and follow its development to the present. I chose to talk about ozone because I do have some milestones to chart the progress of my interest, and because, as I shall show you, it is becoming more relevant, rather than less, as time goes on. I shall also provide some notes on the development of interest in the small airways of the lung; the reason for this parallel history will become evident as we come up to date.

The story of the 'discovery' of ozone by Schonbein in Basel, Switzerland, in the middle of the 19th century is an interesting one. He had worked in England teaching German at a boarding school, and at that time, he met Michael Faraday. Here he must have learned that an electric spark is often followed by a curious smell; when he got back to Basel he later became a professor of chemistry and was able to show that it was ozone (O_3) that was being formed. He did a very thorough job of investigating the properties of this gas, and discovered that it was intensely irritant. Its bactericidal properties became the centre of attention later in the century, and WS Gilbert wrote some doggerel verse calling it "Nature's Great Cleanser". This was unearthed by Bill Linn.

I believe it was the German V2 rocket program that led to the recognition of the ozone layer, starting at approximately 30,000 feet (9144 m) and rapidly increasing to a maximum at approximately 50,000 km before waning. I am not sure of the history of this, but I was first shown German data on the ozone layer on a visit to the Royal Aeronautical Establishment at Farnborough. Our research group, led by Ronald Christie at Bart's Hospital (Farnborough, United Kingdom), was one of the few research groups with an interest in the lung, and we exchanged relevant information. It was there that I learned that the foam rubber in the passenger oxygen masks in the de Havilland Comet had deteriorated rapidly, and that the Dunlop company had suggested that it must be ozone that had caused this disintegration. The 'Comet' was the first aircraft to fly routinely above 30,000 feet. We all realized that we knew nothing of the toxicity of ozone if inhaled at sea level; however, this research was made difficult by the lack of any reliable instrument to measure the gas concentration.

When I went to the Royal Victoria Hospital (Montreal, Quebec) in 1956, with a mandate from Ronald Christie to start a respiratory research unit, the problem of ozone toxicity was one of the questions I took with me. The development of the Mast ozone analyzer (Mast Development, USA) in the early 1960s was a great step forward. I wanted to measure the ozone levels in the latest generation of jet aircrafts and, fortunately, the Chief Engineer of Air Canada at that time, Jack Dyment, was a near neighbour in Montreal. I learned that Air Canada was about to take delivery of their first DC-8, and with him I planned an experiment whereby we would put rubber bands in different places on the aircraft and then replicate the hours the aircraft had spent above 30,000 feet in a box at ground level using an ozone meter; but first I had to go to the Dominion Rubber company in Montreal and get them to supply me with rubber bands, each approximately 0.5 inches (1.27 cm) wide and six inches (15.24 cm) long. There had been several other reports of using rubber cracking as an indicator of ozone concentration. The rubber had to be specially prepared so that it contained no antioxidants.

All of this is described in my paper (Young et al [1]) in the *Journal of Aerospace Medicine*, which came out in 1962. We found the highest ozone level in the tube located in the nosewheel compartment, and the band cracking in the tube taped under the table used by the navigator was slightly less. The tube at the rear of the passenger cabin was affected, but the least of the three. We estimated that levels in the cockpit would average about 50 parts per billion (ppb) for the 270 h the aircraft had spent over 30,000 feet. Some years later, the Federal Aviation Administration in the United States, together with Scandinavian Airlines, began to make systematic observations of ozone in the aircraft on the Seattle-Copenhagen run, and these broadly confirmed these calculations.

My first paper on the effects of breathing ozone came out in 1964. When I became Chairman of the Department of Physiology at McGill University (Montreal) in 1967, I had space to build a plastic chamber, and thus, could study the effects of breathing ozone while exercising, which turned out to be an important innovation (2).

Running in parallel with this work on ozone, we were developing and exploiting the use of radioactive xenon-133 in studying regional lung function. These studies led to the recognition of regional factors involved in nonuniform ventilation distribution – a topic that had been of interest to me

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since I started in pulmonary research in 1948. Using inhaled boluses of xenon-133, and studying the effects of different factors such as body position and age on gas distribution, it became clear that in normal subjects, due to the shape of the pressure-volume curve of the lung, regional airway closure was occurring in the most dependent parts, and this led us to begin to think about small airway function in general and airway closure in particular (3). At the same time, others were getting interested in airway resistance in the small airway region of the lung, and in studies of comparative morphometry, it was clear that the respiratory bronchioles should be viewed as a target region of the lung.

I can also remember being stimulated by dosimetric calculations being modelled by Fred Miller and his colleagues (4,5), which showed beyond much doubt that the highest concentration of inhaled ozone, in terms of concentration per square centimetre of the wall, is in the small airways or terminal bronchioles, and by 1973, I was beginning to talk about small airways as a target area for gases and particles (6).

All of this work, together with the beginning of quantitative morphometry, led me to give a talk at the symposium honouring Julius Comroe on his retirement (7), which I called "The last link in the chain". The idea behind this was that we had spent a lot of time analyzing gas exchange at the alveolar level and studying diseases in which the prime impact was on gas exchange, and we had come to understand the changes in large airways that lead to hyper-responsiveness and mucus hypersecretion; however, the new data emerging on small airways were the last link in the chain and constituted a new area of research of importance as a bridge between these two regions of the lung. This lecture was published in 1977 (7).

Another milestone in this journey was a major symposium held in Copenhagen, Denmark, in 1979 (8). This brought together everyone who at that time was interested in some aspects of small airway pathophysiology, and firmly established that "The last link in the chain" (7) that I had described two years earlier was indeed filling an important gap in our understanding of the lung as a whole. Overall, the symposium proceedings ran to over 250 pages.

I should perhaps pause here to note that the problem of ozone in aircrafts had been the subject of intense enquiry because the aircrew had begun to complain of symptoms that they (mostly correctly) attributed to ozone (9). Modifications to the compressors controlling cabin pressure resulted in cabin ozone levels that were much lower than what I had originally measured.

Meanwhile, the field of ozone research continued its active development. I took an opportunity to be a visiting scholar at the Health Effects Laboratory of the Environmental Protection Agency at Chapel Hill, North Carolina, with Phil Bromberg and my former PhD student Milan Hazucha. We planned a new study to clarify the sequence of events when ozone is inhaled. We were very slow in publishing this work – it did not appear until 1989, almost three years after the experimental work had been performed (10). We found that the initial effect of ozone was to limit the forced inspiration, probably via stimulation of the C-fibre network and a spinal-mediated reflex. The consequent decline in forced vital capacity was accompanied by a decline in forced expiratory volume in 1 s (FEV_1). Thereafter, there was a major direct effect on the small airways, which was quite slow to resolve after exposure had ceased.

It is the case in all research fields that some periods are characterized by a pause in new information and discovery. The 1980s constituted such a pause both in relation to ozone and in terms of small airway research. Work on the air pollution field was about to explode with the demonstration that modern cities were characterized by a statistical association between fine particle pollution (particulate matter less than 2.5 μm in size [$PM_{2.5}$]) and daily mortality, and that both cardiac and respiratory diseases were responsible for this phenomenon. Dockery and Pope (11) drew attention to these emerging data in their review article in the *Annual Review of Public Health*, which appeared in 1994. This association dominated the air pollution field in the 1990s, and concern about ozone faded into the background. The era of interest in small airways appeared to be over, and Jody Wright edited a very useful summary issue of *Seminars in Respiratory Medicine* in 1992 (12), which summarized all the work that had been conducted on small airways. It constituted another milestone along this road. This volume summarized, for the first time, the important ozone work being initiated at the Primate Center in Davis, California; work at this centre went on to demonstrate that remodelling of the terminal bronchioles occurs following exposure of rhesus monkeys to low levels of ozone for the first six months of life.

It seems to be the case with important research questions that they resemble the hydra, in that one head gets chopped off and apparently disposed of, for another to arise and pose a new series of problems. One of the issues that had never been satisfactorily resolved was why repetitive exposures to ozone led to a diminishing response in terms of the decline in FEV_1 induced by a single exposure. This meant that with a daily exposure to ozone, by the fourth day, the response had declined to almost zero. Weinmann and her group at Johns Hopkins (Baltimore, Maryland) began to attack this problem in the early 1990s (13). They showed that the probable reason for this phenomenon was that the inflammation induced by the first exposure led to a protective layer of mucus that diminished subsequent responses. They also demonstrated that the effect of ozone on small airways, as indicated by terminal airflow measurements, occurred independently of C-fibre stimulation (14,15). By the end of the 1990s, studies on several hundred normal volunteers exposed to ozone permitted the consequent loss of FEV_1 in different concentrations to be precisely defined in relation to symptoms recorded (16), and no further data of this kind were needed. A very important development, pioneered in four laboratories in the United States, was the demonstration that an early effect of ozone was to produce inflammation in the lung, as shown by increased protein and changes in cytokines in bronchial lavage fluid after exposure. These changes were shown to persist for up to 24 h after the exposure had ceased. All of this work essentially closed the book on the acute effects of ozone breathing.

At this point, there occurred an unusual episode in this rather wayward history that I am following. At the 1990 Air and Waste Management Association meeting, Sherwin presented some histological data on striking small airway changes in the bronchioles of young residents in Los Angeles, California, most of whom had died violently. There were no details on past medical histories. As far as I know, these data never appeared in North American literature, but 10 years later, these authors published a comparison between the morphological appearances of the lungs at autopsy of 20 Miami, Florida, residents and 18 Los Angeles residents aged 11 to 30 years.

Smoking histories were available for all subjects. The respiratory bronchiolitis was strikingly obvious in the Los Angeles residents and much more severe than the changes in the Miami residents. This analysis was published (in English) in the German journal *Virchow's Archive* (17), and as far as I know, has not appeared elsewhere. In 2003, Churg and his colleagues (18) from Vancouver, British Columbia, published a comparison of morphometric differences in the respiratory bronchioles between residents in Vancouver and Mexico. I annotated this study as follows:

> The study was an analysis of 20 lungs from women in Mexico City (mean age of 66 years) – all never smokers, lifelong residents, no occupational dust exposure and never used biomass fuel for cooking. These lungs were compared with 20 similar lungs (from seven men and 13 women) from Vancouver. The study found that the lungs from residents of Mexico City showed "small airways with fibrotic walls and excess muscle, many containing visible dust". Formal grading analysis (blinded) was conducted. Electron microscopic particle burden on four of the Mexico City cases showed carbonaceous aggregates of ultrafine particles in the airway mucosa. These were considered likely to be combustion products. Aggregates were 0.34 µm to 0.54 µm, and the component individual particles were 0.04 µm to 0.067 µm in size. Muscle hypertrophy was prominent, but there was no basement membrane change. The authors suggested that the demonstrated airway remodelling may lead to chronic airflow obstruction, and in this connection, they cited data from studies of Mexican women in which there was an increased risk of chronic bronchitis and chronic airflow obstruction associated with cooking with wood. The three-year mean PM_{10} in Mexico City is 66 µg/m^3. A possible role for other pollutants was noted, but the authors reported that their findings were similar to those in workers who were occupationally exposed to industrial dust and who did not have other pollutant exposure. Grading system showed scores that were five times higher in respiratory bronchioles in lungs from Mexico City residents, and scores that were three times higher in membranous bronchioles. The study presented excellent and convincing illustrations.

Dr Churg kindly arranged for me to review these sections, and I was amazed at the difference in the appearances of the bronchioles from the lungs from the two regions – after a little guidance I could say without much hesitation where the sample had come from. The authors attributed the differences to the high particulate pollution present in Mexico City. And of course, the ozone levels would have been four or five times higher in Mexico; however, the possibility that some or all of the observed changes were due to ozone exposure could not be resolved.

At this time, the Southern California Children's Health study, initiated and conducted by John Peters and his group at the University of Southern California, began to report the results of their detailed comparison of elementary school children in 12 different communities in the Los Angeles Basin. Rather surprisingly, classic cross-sectional comparisons among these communities did not show any very striking differences in either symptoms or lung function, although the different communities showed considerable variations in the measured standard air pollutants. In spite of these findings, the research group was able to implement its planned longitudinal component. This program got over some of the difficulties of cross-sectional comparisons, and the first cohort followed for four years showed significant differences in FEV_1 and increases in flow rate that were related to the ambient concentrations of vehicle-emitted pollutants where the children were living. A second cohort of children had been enrolled immediately after the first, so that it was possible to confirm whether the same phenomenon was demonstrable in them. The results in the first cohort were exactly replicated in the second. This demonstration that the results of a longitudinal study could be exactly replicated in a second cohort led a high degree of credibility in the conclusions reached. When the results in the two cohorts were combined, they were highly significant, and justifiably made a considerable impression when they were summarized in *The New England Journal of Medicine* in 2004 (19).

What was surprising was that this phenomenon of slower development of the FEV_1 was not related to the ozone level in the different communities (as I had thought it might be), but was clearly influenced only by the package of directly emitted vehicle pollutants and their immediate derivatives. Furthermore, it could be shown that nothing changed if the individual ozone exposures calculated for each child being followed in the study was used, instead of relying only on the ozone measured in the community. Unfortunately, because we know so little about the factors responsible for normal lung development, we are far from being able to suggest what specific pollutant or mechanism might be responsible.

The finding that it was the immediately emitted vehicle pollutants that were important began to be confirmed by a whole series of studies conducted worldwide that indicated that traffic exposure was the important parameter in the associations with acute respiratory outcomes and with increased episodes of bronchitis. The same applied to aggravation of asthma, and possibly to an increased prevalence of asthma; however, because this is a multifactorial disease, it proved difficult to pin down the directly relevant pollutant. As far as ozone was concerned, you may have concluded that the main components were now at hand, because even though many studies had shown a strong association between this pollutant and hospital admissions for respiratory disease (20), and more recently an association between ozone and premature mortality (21), there did not seem to be any major differences between communities in relation to the ambient ozone levels where they lived. The story, however, was not over.

As you approach the equator, the seasonal variation in ozone (ie, at least a twofold difference in ozone between winter and summer in northern latitudes) begins to disappear. Thus, in the city of Brisbane in Queensland, Australia, and in Mexico City, ozone levels are fairly constant throughout the year. This makes it possible to study ozone associations without the confounding effect of seasonality, and it is therefore not surprising that the association between asthma hospital admissions and ozone in Brisbane is very strong (20), and that the association between ozone and daily premature mortality is strong in Mexico City (21).

It is at this point that the two themes I have been following, ozone on the one hand and small airway changes on the other, begin to converge (as the earlier calculations of dosimetry indicated they should do).

It came to be realized that the difficulty lay in separating the acute effects of ozone on the FEV_1 from the later effects

on the small airways. A recent draft of a World Health Organization document on ozone put it the following way:

> "Ozone produces acute pulmonary inflammation at concentrations near air quality standards. Although the development of tolerance occurs after repeated or chronic exposure to ozone. It is now evident that inflammatory events persist even during the development of functional tolerance to ozone. The persistence of a subclinical inflammatory process may promote permanent damage to or remodeling of pulmonary structure..."

The research team at the University of Southern California, conducting the Southern California Children's Study, started in 1990 and had by now developed very strong field teams, and the question was asked as to whether it would be possible to study the prevalence of school absences for acute respiratory illness over a period of several months. Similar studies had been performed elsewhere in relation to episodes of pollution, although none of these had included ozone as a featured pollutant. There were many reasons for being dubious as to whether any clear signal could be derived when there were obviously many confounding factors; and the statistical handling of the data proved to be complex. Nevertheless, the group persevered and finally were able to secure data on over 2000 respiratory illness episodes from children in all 12 of the Los Angeles communities, with confirmation in each case that the cause of the absence had indeed been a respiratory illness (22). The resulting signal, after formidable footwork and refinement of the complex statistical approach used, was a strong one. It showed that an increase of 20 ppb in the ambient ozone in the region where the child was living for 48 h before the absence was associated with an increase of 62.9% for illness-related absence rates, 82.9% for respiratory illnesses, 45.1% for upper respiratory illnesses, and 173.9% for lower respiratory illnesses with wet cough. The effects were larger in communities with lower long-term PM_{10} values, but PM_{10} and nitrogen dioxide levels were not associated with any increase of risk.

An acute respiratory illness following ozone exposure may be caused by a number of mechanisms. For example, ozone interferes with macrophage function, and this may intensify the response to a common or garden infective agent, particularly viral in origin. If ozone induced a degree of small airway inflammation, a subsequent infection may well be more severe. Therefore, there is plenty of evidence indicating biological plausibility in the case of a 'respiratory infection' following a higher ozone exposure. The data from this study formed the basis for an economic estimate of what it represented in terms of dollars (23). The authors calculated the consequences of the observed reduction in ozone from 1990 to 1992 and 1997 to 1999 for rolling three-year periods. They found that overall estimates of the number of children who had exposures above 70 ppb on weekdays, from 10:00 to 18:00 indicate a reduction from 83 million exposures per year in the period of 1990 to 1992 to 17 million per year in the period of 1997 to 1999. The baseline population was the cohort aged five to 18 years residing in the south coast air basin in 1998; there were 3,283,429 children in this cohort. Between these two intervals, when ozone declined, "the economic value of fewer school absences ranges from $156 million annually to more than $330 million annually, with a best estimate of $245 million. This represents a benefit of nearly $75, on average, for every school child in the region" (23). The overall estimate should be considered conservative because of the following:

- Only one day of school absence per episode was assumed;
- Only 8 h ozone values above 70 ppb were taken into account; and
- No estimate was made of medical consultation or medication costs.

This calculation represents a highly credible estimate of the economic burden of current levels of air pollution in one polluted community; and there is no reason to suppose that it would not be operative in any community with comparable ozone levels.

One of the most difficult challenges is to try and devise ways to study the long-term effects of living in a higher oxidant or higher ozone atmosphere. Ira Tager, from the Department of Epidemiology at the University of California, Berkeley (24), had the idea some years ago of examining incoming students to that campus with questionnaires and pulmonary function measurements, concentrating particularly on indexes of terminal airflow velocity. His first pilot study showed the feasibility of his design, and in 180 students aged approximately 19 years, who were all nonsmokers, he found a difference in mean terminal airflow velocity between those who had grown up in high oxidant levels in southern California, and those who came from northern California and the Bay area. The lowered airflow velocities were not associated with differences in PM_{10} or nitrogen dioxide exposure. He was then funded to repeat the study with a second cohort of entering students, and he sent me the manuscript of this study a couple of days after I had been invited to give this lecture, and it has now been published (24). The following is my annotation of it:

> The study group consisted of 255 incoming students (58% women) to Berkeley who had never smoked, and who had grown up either in the Los Angeles or the Bay areas around San Francisco; their mean age was approximately 19 years. Geocoding of places of residence allowed calculation of average ozone exposure. There were no associations between any measure of pulmonary function and history of asthma before the age of 12 years, history of pneumonia, bronchitis, allergic conjunctivitis or rhinitis, or ETS exposure. The calculated ozone profile was similar in men and women. Correlations between PM_{10} and ozone exposure were high in several groups. Results showed "consistent inverse associations between increasing lifetime exposure to O_3 and FEF_{75} and FEF_{25-75} for men and women" (24). Associations with nitrogen dioxide and PM_{10} were also significant, but reduced substantially when ozone was included.

So my two interests of ozone and small airways have come together. Of course, I cannot prove that what is being induced is chronic bronchiolitis, but the evidence seems strong enough and consistent enough to me to urge that we must watch, extremely carefully, the ozone levels to which we are being exposed. This is made more urgent by the fact that background ozone levels above the Atlantic Ocean have been observed to be increasing over the past five years; in fact, many areas of the United States and Europe now have ozone levels that exceed their current or proposed standards. Moreover, in the Fraser Valley of British Columbia, to bring it right home, the average 8 h ozone levels in the summer have been slowly rising over the past 10 years. Due to the sharply rising increase in nitrogen

dioxide emissions in Asia, and particularly in China, the background levels of ozone coming to the west coast of America across the Pacific Ocean are predicted to rise slowly but steadily.

I chose to go back over my interest in ozone and small airways because I think we should have a cadre of chest physicians well-enough informed about these two converging topics to be able to watch future scenarios with intelligence and perspicacity. My hope is that this record of my interest in this problem will encourage others to become knowledgeable about it.

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