THE CHANGING MORTALITY OF ASTHMA

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MODERATOR: I'm absolutely delighted that we have such a distinguished speaker to address us at this morning's session. Professor Malcolm Sears is one of those individuals who, I think we can honestly say, in his career in medicine has made a very important contribution in his specific area, that being in the whole area of identifying the changing trends in asthma mortality. Dr. Sears is a distinguished researcher and educator and you'll find him to be a delightful speaker.

DR. SEARS: Thank you very much. It's a pleasure to be here. Five years ago, this topic would have been doom, gloom and bad news. I think we are emerging from that and looking at some good news where the trends are becoming favorable, because we now have a much greater understanding of what had caused some of the adverse trends about which we have been gnashing our teeth and wringing our hands for several years.

I need to go back to some history and take you through a number of studies that have led us to what we now understand, at least a sizeable part of the problem of asthma death, and then to look at what is now changing and which way trends are going, hopefully for the benefit of the asthmatic.

In the mid 1960's we first became concerned about an epidemic of asthma deaths which occurred in New Zealand, Australia, England, and Wales. It did not occur in Canada, the U.S., and other countries. This came and went again largely by the late 60's and early 70's, although the New Zealand figures stayed quite high. At that time there was a lot of speculation that this increase in asthma death was associated with the launching of a high-dose, high-potency beta-agonist or adrenergic agent, isoproterenol-40. Because it was marketed in those countries where there was an increase in deaths and not marketed in others. It seemed that there was a likely link, but there was a lot of debate. No appropriate studies were done. The issue was argued about for 20 years. People said that it was just that we diagnosed more asthma because we had a more powerful beta-agonist to show that people improved, and therefore we made a diagnosis of asthma and this was just an artifact. False negatives and false positives have been looked at in New Zealand there was a marked increased in asthma death rate in young people, 5-34 year olds. This was two years before the change of the International Classification, and in any event, the ICD change does not effect young people to the extent that it does the older ones. At that time we began looking at what was happening. We were concerned that in New Zealand we were seeing an increased number of asthma deaths and did not understand why. We started looking at other countries. In the U.S., for instance (this is not expressed as a rate, but as absolute numbers of deaths by ages), starting at young age you'll note that from 1973 to 1979, this is in fact tending downwards. In 1979, we moved from ICD-8 to ICD-9, and that did bring about an increase which is an artifact of coding, because of inclusion of bronchitis with asthma now under the general heading of asthma, whereas previously, somebody dying of bronchitis with asthma was coded as dying with bronchitis. From 1979 onwards, that same coding led to a final certification of asthma. So this increase in 1979 is artifact. However, that can't explain what's happened since. One of the things that has confused all of us is that there seems to be a downward trend, followed by an upward trend, and the change occurred about the same time as the ICD change was made. That was very confusing, and it took a number of years to realize this could not be accounted for simply by the ICD change. If it was, we'd expect it to come down, then up, then stay flat or come down. In fact, it's gone up.

If one looks at the young age groups where we know that the diagnosis is more accurate, it's perhaps even more striking. The numbers are smaller, but again in the U.S., people up to age 35, there is a downward trend through the 1970's, an upward trend through the 1980's. In this age group, the effect of the ICD-9 change is essentially nil, because people under 35 when they die of asthma are coded as dying of asthma; bronchitis doesn't usually get much of a mention. Now, in Canada, the same trends seem fairly flat in the early 70's, but tending upwards.

What effects these statistics? Somewhere in the midst of all these is the truth. But true asthma mortality can be modified up or down by accuracy issues, the false positives and false negatives, the change in the ICD code. False negatives and false positives have been looked at
in a number of studies and in particular, I just want to summarize the National Asthma Mortality Study we undertook in New Zealand from 1981-1983. I never want to do another study like this again, and I think we won’t need to because we have further information. This was a very large study where we looked at all 492 people said to have died of asthma over a period of three years and tried to ascertain firstly, did the person actually have asthma? In 88%, we thought the answer was yes. Some clearly did not have asthma, and a few we couldn’t make up our minds about. But secondly, having said the person had asthma, did the person actually die of their asthma, or did they die with asthma but from some other cause? Only 67% actually died of asthma. When one looks at the accuracy, there was a very striking relationship with age. In young people, this is the number of deaths which were coded by the National Health and Statistics Center as asthma deaths. These are the numbers for the same individuals which we as an expert panel looking at all the information available from family interviews, doctor interviews, hospital records, autopsy records, and so forth, said were asthmatics and asthma deaths. And you can see up to age 34 we have 100% correlation. It’s good right through to the 50’s, and if one averages all this, we’re looking at over 90% accuracy. But when you get into the older age groups, particularly over age 65, you are getting into trouble. Over age 70, flip a coin to decide whether this is accurate or not. For that reason, in our studies of asthma deaths, we have concentrated on young people, because accuracy is high and the ICD code changes and other labelling and diagnostic shift do not effect young people nearly as much as they effect older people.

This is a figure that was in a paper published just a few months back, but it illustrates what we saw in that New Zealand study: two types of asthma death. Type I has a lot of background problems and difficult asthmatics, difficult families, psychosocial problems, gradually worsening asthma, bad management of asthma, both by the patient and their doctors, poor use of steroids, delay in getting care, and the individual dies. Type II are the people we thought we were doing well with, including some of my own patients, that I thought I was managing their asthma quite well, and they died suddenly. This is really what got me involved in this area, first of all, because two of my very well-managed asthmatics died within hours of having an episode of asthma. One died within minutes. I didn’t understand this at all.

We have two different types. This is the model of increasingly worsening asthma, badly managed. On the other hand we have the somewhat less frequent, sudden unexpected asthmatic death, usually in people who have severe asthma, but not with these other background factors. From that New Zealand study, we listed a number of things which we thought indicated a high risk of asthma death. Now this was an uncontrolled descriptive study. We simply looked at this individual who died of asthma and looked at factors which seemed to be common, factors which we thought should not have happened, or which we would have done differently, in retrospect, of course. It’s always easy to be wise after the event. But the factors which seemed to be important were poor patient compliance, discontinuity of care, the patient who jumps from doctor to doctor or simply gets their management from emergency rooms, a history of having had previous life-threatening episodes, especially intensive care admissions, ventilation, intubations, and so forth. It was fairly clear that in many of these people, the severity was underestimated, both by the patient and the family and their doctors. Interestingly, the patient’s family often said, "Yes, we thought the asthma was bad enough he might die." Whereas the doctors often said they never thought the individual might die of their asthma. Underassessment of severity was also highlighted by the infrequent use of any objective measurements. Lung function tests were notable for their absence.

In terms of treatments, the factors we were concerned about were over reliance on the use of beta-agonists...

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...and died often having used 10, 20, 30, or 100 puffs of the beta-agonists in the hours before death. But also there was a lot of long term frequent or heavy use of beta-agonist, including nebulizing use in about 25% of those who died. On the other hand, steroids seem to be under utilized, both long term and at the acute event. Half of those who died of asthma had seen a doctor with ample opportunity to give them a dose of steroids in their final and fatal attack, and it had not been given. Also, delay in seeking help was one of the factors.

All of that said we had a problem; we had severe asthma; people are dying, we were not doing very well, and we had not yet come up with a clear indicator of the reason for the increase in asthma deaths, or a real feel for what had caused this new epidemic of deaths; we said it was multi-factorial.

Well, perhaps it is, but I think we now have some further factors coming in. These further factors came from a study which raised a lot of controversy. They used individuals who had been studied in that National Asthma Mortality Study, but extracting from hospital admissions at the same time a series of controls. It was an attempt to convert the descriptive study into a case-
controlled study. This first paper was published in 1989 in the *Lancet*, where they took the individuals from the National Mortality Study, restricting it to the younger age group, 117 deaths in that age group, took 4 controls for each case from those who were hospitalized, and then looked specifically at the odds ratios for the use of different drugs. They came out with an odds ratio for fenoterol (which is not available in the U.S., but is available in many other countries as a fairly potent beta-agonist) which exceeded 1, significantly so, and therefore is a significant risk factor associated with death. On the other hand, solbutimol, albuterol showed an odds ratio less than 1, appearing in fact, protective.

A lot of us had major difficulties with this study, partly because of the selection of controls. All of the cases were very well validated, documented, and we'd studied each case individually. The controls were much less well validated; there were a whole lot of methodologic issues that raised our concerns about whether this was believable or not. One of the major arguments against this study was severity. Fenoterol had been marketed after solbutimol; it came out at 200 micrograms per puff, rather than 100, and many of us knew that we had taken patients who were not doing well and converted them from solbutimol onto this newer, longer acting, more potent fenoterol. These were the individuals who, understandably, would be at higher risk of death anyway, because they were not doing well with their asthma. One of the possibilities here was that we were simply looking at confounding severity, that the higher risk associated with the more potent drug was because the worse asthmatics were on that drug.

To try to answer that they looked at other factors and tried to modify for severity. So they said the use of three or more anti-asthmatic drugs, having had a hospital admission in the last year, using oral steroids were markers of severity, and said if it is confounding by severity, when we adjust for those markers of severity, the odds ratio ought to come down. In fact, it goes up. When you add two or more of those severity factors, the odds ratio becomes very high, and that argued strongly that the risk associated with a potent beta-agonist was not due to confounding severity, but was due to the effect of that beta-agonist. They postulated that this meant there was a toxic cardiac effect, arrhythmias and so forth, from overuse in the minutes leading up to death, which was the mechanism that had also been postulated back in the 1960's with the use of high-dose isoproterenol.

A lot of us were uncertain about that and criticized the methodology. We didn't really know whether that should be believed or not. So the authors did a second study from 1977-1981, looking at exactly the same things, but this time they confined it to people who'd had a hospital admission prior to their death, and then matched those with cases who had also had a previous hospital admission, trying to answer some of the concerns over matching. They found very much the same thing, with a higher risk for fenoterol, a lower risk for solbutimol. Again, when one matched for severity, there was an increasing odds ratio.

Well, we criticized that one not quite as much. But there were a number of methodologic issues in that, which led to uncertainties. So the group in Wellington, led by Richard Beasley, went on and did a third study which answered many of the methodological issues. It still leaves a few things up in the air. They looked at 112 individuals from 1981-1987 in this younger age group who died with a hospital admission in the last year. Then to try to answer the critics, they took two different sets of controls, saying if you don't like one, look at the other. In fact, the answers came out very much the same, whichever set of controls you use, whether they had a hospital admission with a prior admission or just a hospital admission. Again, the same effects are seen: fenoterol comes up with an increased risk or increased association with death, solbutimol a decreased risk. When you adjust for severity, this risk does not go away, although the increase with severity is not as obvious as it was in the first two studies. We think this probably is about as good a result as you can get from that kind of a case-controlled study, given difficulties of retrospective records and so forth.

The first study led to further international investigations. Buren Engleheim, whose drug was under suspicion, established a much larger very well conducted case-controlled study in Canada in the province of Saskatchewan, which was chosen because the health records are computerized. What they did in this project, which was headed by Walter Spitzer, was to take the whole population of Saskatchewan, and confine it to the 2-54 year age group, looking at 1980-1987. Because all drug prescriptions were computerized, they could identify everybody that had a prescription for an anti-asthma drug, 68,000 of those. So they took those who'd had ten or more, to reduce the numbers and also make it likely that these were people with asthma. A lot of people can take one drug, but if you go back ten times to get an anti-asthma drug, it's likely you've got asthma. They ended up with 12,000 individuals with asthma, or using anti-asthma drugs. Then they looked prospectively, if you like, because they identified these individuals from their drug prescriptions, and then followed them forward through the years 1980-87 to see how many died. They found 44 who died and 85 who
had what they termed near death, which again was intensive care admission, intubation, ventilation, the kind of scenario which can be expressed by saying thirty minutes later, they would have been dead. For each of those 129 deaths and near deaths, they established controls, between 2 and 8 controls for each case, matched on a number of factors to try to overcome issues about where they lived, what their social status was, numbers of hospitalizations, etc.; the controls were at risk at the same time as the deaths. Then they looked at their drug prescriptions. Now these are drugs used, because they've actually picked up prescriptions, and therefore the expectation is that they were used. Just looking at asthma deaths, fenoterol came out with a very high odds ratio associated with death. There was an odds ratio of 9, with a 95% confidence, which is wide, but the odds ratio is quite high. But, now the other beta-agonists, particularly salbutamol and theophylline, come up with odds ratios of 3, not less than 1 as in the New Zealand studies. Now all beta-agonists look as if they carry a risk, not that one is a risk and one is a benefit.

However, I'd also point out, very importantly, the use of corticosteroids did not increase the risk of asthma death, and the use of inhaled steroids likewise. In fact, a further analysis just looking at inhaled steroids alone indicates that that is protective against asthma death when used in more than occasional dosage.

If this risk of death was due to more severe asthma, one would expect the use of steroids would give a high odds ratio, because the patients with worse asthma are more likely to have used corticosteroids. So again, it looked likely that there was a link with the use of drugs.

Even more strikingly, they went on to look at a dose response effect, looking at either deaths and near deaths or deaths only. If one takes not using inhalers as the reference value of the risk of one, an odds ratio of one, an individual who uses between one and twelve inhalers per year, in other words up to one canister per month, has a risk of about 4. People using one to two inhalers per month, the risk goes up markedly. When you're using over two inhalers per month, the risk, particularly for deaths, becomes astronomical. The same increased risk with the increased use applies to both of the beta-agonists, and as Walter Spitzer is inclined to say, "It's certainly higher for fenoterol, but this person drowned in 113 feet of water and this one in 29 feet of water, but they're both dead."

This indicates that the more beta-agonist that is used, the higher the risk of death, and it applies to both of the beta-agonists in common use. What does that mean? It could again be said that severity is the only issue. There's a paper which appeared a couple of months ago, where the authors had gone to their group and looked at markers of severity and have suggested that it did not effect it, that when they adjust for all they can adjust for there is still a direct association with the amount of beta-agonist used that is not accounted for simply by severe asthma.

However, at the same time all these studies were going on, we were undertaking a further study regarding the concern that asthma seemed to be getting worse. We were seeing more hospital admissions; they were just as sick when they were admitted, so it's not that we were admitting people with milder asthma. The sales of anti-asthma drugs were going up. We'd done studies to see where they were being used, and they were being used for asthma. Yet every time we did a population study, we'd wring our hands and say asthma is still under-treated. It looks like we're seeing an epidemic of worsening asthma. The question is, "Why?"

At that time I had made some small independent observations based on a few people I had been managing in my practice where I had noted substantial improvement when I took them off beta-agonists. I was doing this for the purposes of other studies, but it raised the whole question, "Does the use of beta-agonists actually make asthma worse?" Now this was theoretical, and I put this up to the Medical Research Councils to study. One of the people who reviewed it said, "It's a wonderful study, but what a stupid idea." Anyway, we did this study, and the answer has created a lot of ripples. What we set out to do was to answer the question, if you take a beta-agonist two puffs four times a day, which was standard management for us, and in many places, does that improve your asthma or not. Our underlying fear was that it made it worse. What we did was the typical randomized placebo controlled crossover study. It was a long study, each treatment period for six months. We gave them fenoterol as a dry powder, two puffs, which was 400 micrograms, four times a day, or a matching placebo. They could use a known beta-agonist by aerosol if they needed for relief of symptoms. We kept them on whatever dose of inhaled steroids they were on, keeping that constant throughout the whole study, and got them to record flow rates and symptoms. In the end, everything else being kept as constant as possible, were they better controlled during the period of regular beta-agonist treatment, or better controlled if it was used only as needed? The answer was, during the last 16 weeks of each of these treatment periods, looking at each individual in terms of their flow rates, need for steroids, use of rescue beta-agonists, symptoms, we determined for each individual which period was bet-
ter, before we broke the code. We then broke the code, and even though that was our hunch when we started, we were still astonished how strongly the finding came out that the regular period with fenoterol was favored by only a small percentage, and a much greater percentage were better when using a beta-agonist only if needed, a highly significant result. In other words, asthma was worse in the majority when they took a beta-agonist regularly, all other things being kept constant.

The measurements of lung function were lower during regular treatment. The measurement of airway hyperresponsiveness was also low. In other words, it took less to make the airways twitch. These are all indicators of worsening asthma. Peak flow rate was lower, the variation in peak flow from morning to evening was higher. It took far shorter time till they came to the first exacerbation; in only 33 days they were having an exacerbation on average, versus 66 days when they took it as needed. We had six individuals who needed to be hospitalized or to drop out because of severe asthma; five of those six occurred during regular treatment. There were small differences in prednisone use with more exacerbations. In terms of exacerbations, if one does the survival curve from the start of the study to the time of the first exacerbation, you'll see there is no difference for the first couple of weeks, but then more exacerbations occur on regular beta-agonist treatment than as-needed. This was a highly significant difference.

We were convinced from that study, that using fenoterol, two puffs four times a day, made asthma worse. Do we have any other evidence for that? There was a study that was going on at the same time for a different reason altogether, looking at comparison of beta-agonist with inhaled steroid, but we can extract some of the data from that. They used another beta-agonist, turbutalene, and they looked at those individuals who were given turbutalene on a regular basis for two years. What they found was that they needed more turbutalene at the end. In other words, they were having more symptoms to need to be rescued. The symptom score had increased; the lung function went down. So, this is another independent study, using another beta-agonist on a long term basis, showing worsening of asthma control.

Here is a study of children, showing exactly the same thing. Again, this was a study for which the primary purpose was looking at steroids versus beta-agonists. If you look at Group B, who were just getting beta-agonists, half of them had to drop out of the study, because their asthma was so much worse. Lung function went down; peak flow rate didn't improve, but their PC20 went down. In other words, they had evidence of increased asthma, worsening lung function, increased airway responsiveness with regular use. This time we were looking at solbutimol.

So there were three of the common beta-agonists with studies where the data interpretable as showing regular use made asthma worse. Just in the last few weeks, another study was published, again with solbutimol. This time they used a lower dose, only two puffs three time a day for only three weeks. What they showed was that peak flow rate dropped, variation increased, there was increased nocturnal wheezing, lung function went down, and histamine responsiveness increased, all showing adverse effects of regular beta-agonist.

Finally, a study of Peter Sterck's group in the Netherlands showed that if you give a beta-agonist before you give a challenge, with histamine or with methacholine, as you expect, you shift the dose response group. This is the untreated histamine challenge, showing somebody with asthma as you give increasing amounts of histamine, the airway narrows. If you give beta-agonist, you improve lung function, you shift this curve, but for the asthmatics, which is this group, they show that once you break through that protection, you still get airway narrowing, and in fact, this downward slope is even steeper. So it looks as if you get partial protection, but if you break through that because of a high challenge, and this might be an allergen challenge, an exercise challenge or whatever, that once you break through that protection, you might be at greater risk because of the use of beta-agonist.

So what do we think is happening and how does this link with asthma deaths. This is my view of what's happened, it also tells you why we hadn't noted this until we looked for it, because the shift is relatively small, sustained by a lot of people who stand up in audiences and say, "I've been treating asthma for 30 years, and I don't see my patients all dropping dead." What I think we're seeing is a small shift in severity of asthma because of the frequent use of beta-agonists. It may only apply to a certain subset; it may, for instance, only apply to atopic, as opposed to non-atopic, although I'm not really sure we can say that. A small shift overall will make very little difference to what most people see. Those I'm treating, those that family doctors are treating, most people that specialists are treating, but a small shift here will make a shift here. You only have to move this curve over a little bit, the same area under the curve, but look at the increase in ICU and in fatal asthma. This is a bit hypothetical, if you like, but what I think is happening is this; this is my hypothesis, for which I think there is now good data. For all sorts of
reasons people get asthma, and they get increased air-
way hyper-responsiveness, and so forth. Treatment in
the past when they had mild asthma is to give beta-
agonists, standard practice for many years; if there is a
tiny bit of bronchospasm, treat it with a beta-agonist. In
some individuals, if not in all, the use of beta-agonist on
more than an occasional basis can convert mild asthma
to a bit more asthma. When it gets a bit worse, what do
you do? You give more beta-agonist. And when a more
potent beta-agonist comes along, you change to that,
and you may shift people around here.

Now, is this extreme? We had six hospitalizations or
drop outs in six months who started with mild asthma,
and we pushed them around that curve to having se-
vere asthma, needing hospitalization. When you get to
that state, you have high doses of everything, including
steroids. But one of the factors that came out of our
study was that the use of steroids did not block this
adverse effect of regular beta-agonist. I think this is a
model which may explain why we’re seeing more se-
vere asthma, more hospital admissions. When you get
into hospital, you get everything again; you get nebu-
lizers thrown at you, and so forth. And we end up with
an increased number of people in this vicious circle with
worsening asthma, getting more treatment, which in
turn, if it’s more of the beta-agonist, high doses, nebu-
lizer doses, may be aggravating the disease. If there are
more people with more severe asthma, then there are
more people at risk of death. You only have to be at the
wrong place at the wrong time in the wrong circum-
stances and you’re at risk of fatal asthma. I think the
increase in asthma deaths is not so much due to chang-
ing circumstances as to more people at risk, for which
the circumstances are adverse at times.

Others would say they haven’t seen any sort of a prob-
lem with this at all. I take this from the U.K. data, where
the Committee on Safety of Medicines in the U.K.,
looked at all the information when our study came out
and one or two other studies and said they didn’t think
there is any sort of a problem. Here is what’s happened
to the sales of beta-agonists in the U.K., and this is
what’s happened to asthma deaths – no relationship at
all. As I looked at that I said, “This is bizarre, because I
track asthma deaths in about 20-25 countries, and I
know they’ve gone up in the U.K. How can they draw
a flat line, when it’s gone up?” When I looked at it again
I noticed what they’ve done. Look at the scales. Here is
the scale for the sales of asthma drugs, 0-12 in millions,
which is fine, because that’s the magnitude. They put
the same scale, 0-12, for deaths, and if you put a very
big scale for something that’s happening on a small
scale, it’ll look like a flat line. If you plot that again this
way and put asthma deaths on the scale where it’s
happening, 2.4-4, and drug sales here, you can make a
case that asthma deaths have gone up as drug sales have
gone up. Now neither of those proves or disproves; I’m
just saying be very careful what scales people draw
when they want to make a point. In the U.K. there has
been an increase in asthma deaths, which has paralleled
the increase in the use of beta-agonists. It doesn’t prove
it.

What we now have is a number of studies that show
that the regular use of beta-agonists has increased air-
way hyper-responsiveness. A study published just last
week from Don Koquat’s group in Saskatoon showed
that two weeks of regular beta-agonist doubles the air-
way allergic hyper-responsiveness. That’s powerful
stuff that may explain why the frequent use of beta-
agonist makes people worse, and if you have twice as
much response to allergen, if you happen to meet up
with a potent allergen and you’re in the wrong place at
the wrong time, maybe that explains some of the sud-
den deaths from asthma.

I think we’re looking at a class action of the beta-agonist;
I think they all do this. The effects, and what we see in
terms of asthma death, is related to the potency. I think
we saw the 1960’s epidemic when isoprenaline or iso-
proterenol-40 was introduced – five times the strength
of isoprenaline, and we’ve seen the second epidemic
with fenoterol, which was a more potent beta-agonist
than its competitor. But it doesn’t indicate the other
drugs are benign. It indicates that the more potent beta-
agonist you use, the more likely you are to see this effect.

If this hypothesis is true, can we do anything about it?
What happens if we try to break this vicious circle?
We’ve talked about this, and people have made all sorts
of remarks about it. One who reviewed a paper I wrote
on this said, "If they are wrong, we’re going to be in for
an even worse epidemic; if we stop beta-agonists, and
these fellow are wrong, we’re going to see disasters."
Well, here is what we have seen. In New Zealand in
1990, as a result of the emphasis on taking people off
potent beta-agonists, and in fact, because of the with-
drawal of the most potent beta-agonists, we have seen
hospital admissions drop 40% for asthma; ambulance
use has obviously gone down. Death rates have fallen
markedly. This is very striking.

This is what had happened; here is where fenoterol was
introduced in 1976. This was our baseline. This is the
epidemic where we didn’t know what was happening;
we were studying it. We said we’ve got bad asthma, we
need more steroids, we need faster ambulances, we
need all sorts of things, and we managed to bring the
death rate down a bit by education and steroids and all
those other things. Then we finally said this is fenoterol, with a lot of debate, but the Health Department, in its wisdom, put a warning on it in 1989, and finally took it off the market in 1990. The asthma death rate is lower than it’s been since 1960. That’s too abrupt to be explained by education or steroids or anything else. I think it has to be a direct effect of drugs. It may be that that’s because we have all our severe asthmatics now getting to hospital, rather than dying at home. But this is intensive care admissions, to one of our big units, that’s over the space of 1989 and onwards; intensive care admissions have dropped off markedly. So there’s been a whole shift in severity of asthma, and it’s seen both in hospital admissions and in deaths. Again, this is the time when the intervention occurred, now looking at the 5-54 year olds, admissions very stable, suddenly plummeting. Deaths coming down a bit, but staying fairly stable here for a number of years in spite of our best efforts, plummeting. So overall we know what the problem has been, at least in good part. I’m not saying this explains all asthma deaths, but I think we have seen an increasing severity of asthma which has been reflected in more admissions and more deaths, because we were relying on beta-agonist treatment as maintenance therapy for asthma. Now that we’ve recognized that it is hazardous, and certainly not everybody accepts that yet, but most of the guidelines coming out now for management of asthma say the less beta-agonist you use, the better.

The trends are becoming much more favorable. Where potent beta-agonists have been pulled off the market, the trend changes are dramatic. I think we will see in the next few years, as the switch goes away from using beta-agonists, even the commonly used salbutimol, the trend will be a downward use, I am fairly confident that we’ll see downward trends in severity reflected in both admissions and death. Thank you.

DR. RAYMOND GILL, Mercantile & General, London: Congratulations, Professor Sears on this presentation. As we saw in your slide, the number of prescriptions for anti-asthma drugs going up at about a 45-degree slope, and we know in England that asthmatic symptoms are going up every year. Would you like to speculate as to why that might be?

DR. SEARS: Well, there are two issues here. If you’re asking if there’s an increase of prevalence of asthma per se, yes, there is, but it’s not very striking. But there is an increased baseline asthma prevalence. That might be due to issues such as the in housing, allowing more house-dust mite exposure, and so forth. I think possibly it also relates to the increased risk because mothers smoke much more than they did 20 or 30 years. Those issues may be changing the overall development of asthma in early childhood, which will obviously lead on into adult life. But much more so, we’ve seen an increased severity of asthma. The hospital admissions in some places went up ten-fold over a ten- or twenty-year period. That’s not a change in prevalence; that’s a change in severity. I think this beta-agonist issue is probably the major explanation of that severity shift.

DR. IVAN T. BECK: I have a physiological question. Is it possible that when you use a beta-agonist, there is a negative feedback mechanism to the receptors? Therefore, when you take it under higher doses, suddenly it becomes an alpha-agonist, and acts as an alpha-agonist, and actually has a broncho-constrictor action.

DR. SEARS: Again, there are two or three issues in this. These are fascinating mechanistic questions which we and others are looking at now. What we have said is that our first study was to answer the question of is there a problem with beta-agonist. The answer is yes. Now we’re trying to sort out why and what. Clive Page has done some interesting study on isomers. For instance, salbutimol is a mixture of a positive and a negative isomer. The positive isomer is a broncho-constrictor; the negative isomer is the one we want. There is some evidence now that shows that the broncho-constrictor isomer lasts longer in the body than the broncho-dilator isomer. So in other words, you get your broncho dilatation, which wears off, and then you’re left with a rebound broncho constriction. That’s one of the possibilities. The shift from being a beta-stimulant to an alpha-stimulant, I’m not sure there’s any data for that, but it’s an interesting concept. The issue of tachyphylaxis to the beta-agonist effect has been looked at for years in terms of smooth muscle cell tachyphylaxis. And while you can show it, it’s minimal, and it probably doesn’t explain what we’re seeing. But we’ve been looking at the wrong organ. A couple of studies in the last year have shown that there is cell tachyphylaxis; both indicate that the frequent use of beta-agonist may up regulate the mast or allergic hyper-responsiveness. This issue of being more at risk from a challenge because you had a previous beta-agonist I think is one of the areas that looks highly promising as an explanation for the mechanism.

DR. MARTIN ENGMAN, Lincoln National: Some studies have looked at the point prevalence of asthma and its severity on a county by county basis, and have shown that there is quite a variation from one county to another, and that the prevalence hasn’t necessarily uniformly increased across a large geographic area. I’m certain that many factors may contribute to this, one of which is air quality. Do you have any comments about
various epidemiologic factors that might be responsible for this variation on a local basis?

DR. SEARS: Firstly, I think it's uncertain how much of a variation there is between countries is real and how much depends on how the studies are done. At the present time, as you probably know, there is a big international study going on in about 20 countries, using the same questions, the same methods, to answer this issue, if there is a difference in the prevalence of asthma between Denmark, U.K., Australia, Canada, etc. Some of the differences may be methodological rather than real, but there probably are going to be differences. One of them may well be house-dust mite exposure. For instance, in Australia, which is said to be the house-dust mite capital of the world, everybody is exposed to much higher levels than they are in many other parts of the world. The pollution question has been addressed, and the data have been found wanting, really, in that there is very little evidence that outdoor air pollution is a factor in asthma. Many parts of the world are highly polluted, and asthma rates are low. Also, in the last 20 to 30 years, many places have cleaned up their pollution, and the asthma rates have gone up. So the correlations are very weak. In Hamilton, just down the lake, a study was done some years ago, looking at children who lived in the highly polluted area of the city versus the other end of the city. There was no difference in asthma at all, and the only thing that really identified the risk there was whether or not the mother and father smoked in the home, not which area they lived in. So I think the outdoor air pollution is probably not a very important factor, if at all.

DR. THOMAS ASHLEY, Lincoln Benefit Life: Do you think that this will extend to the use of oral beta-agonists, and also will it extend to the treatment of COPD in older patients?

DR. SEARS: These are two questions we can't answer. As far as the oral beta-agonists are concerned, I see no reason why it should not extend. There is one older study in the literature, going back 10-15 years, where an oral beta-agonist given for six weeks caused a fall in lung function, but it hasn't been studied. The COPD issue is one that has to be addressed; we don't have an answer. We've got a study ready to go; I don't know whether your Academy has funds for research. We've got have of the money we need, so if anybody can help us raise another $80,000, we'll get that study off the ground. It's ready to go; it's funded by the MIC of Canada to a tune of 50% of what we need. It's a study desperately needing to be done to look at whether these effects apply to COPD or not. It may be a totally different disease process.

DR. SUSAN SOKOLOSKI, CIGNA: The decreasing use of beta-agonists is probably going to lead to increasing use of cortico-steroids. Do you have any concern about possible adverse effects of that, especially in children.

DR. SEARS: In fact, one of the fascinating things we've found as we take people off high doses of the beta-agonists is that many of them need less steroids, rather than more. I would have said exactly that same thing a few years ago. "We need to switch from beta-agonists onto steroids." But as we've taken people off high doses of the beta-agonists, their asthma improves just by doing that. Many of them are now maintained on much less steroid. I have patients who had been on prednisone for 20+ years, who are now not needing any prednisone, and are taking only a modest dose of inhaled steroid, and hardly needing a beta-agonist at all, and whose lung function is better than when they were taking prednisone, 15-20 milligrams per day. That's part of the answer; people can be improved by reducing the beta-agonist, which reduces severity of asthma, which reduces the need for steroid. On the other hand, since we're now saying instead of beginning treatment with beta-agonists, we should begin with steroid, there will be more steroid being used in mild asthma. The evidence is that low or moderate doses, up to 1000 micrograms a day, have no long term adverse effects, even in children, at least up to 600 micrograms in children. High doses do get absorbed, but again, the question is if its' better to use a high dose of steroid, at least initially, get it under control, than to go the other way, which we've done in the past, which has got us into further and further trouble. Our tendency is to recommend using a high dose of inhaled steroid to get it under control, then bring the dose down to the minimum that you need. The vast majority of asthmatics can be controlled on quite low or moderate doses of inhaled steroid, which I think is safe, long term.