DR. BRUCE ROWAT: A meeting such as this would not be complete without a discussion of urine. At one time diabetes melitis was called the "pissing disease," and its diagnoses was made on the basis of the tasting of the urine by the treating physician; the sugary content, of course, confirming the diagnosis. Just as our forbearers in medicine were interested in urine, we're very interested in the insurance industry with regards to issues such as proteinuria. We're very fortunate this morning to have an expert in this area, an individual who has a distinguished record, both as a researcher, as a nephrologist, as well as a medical educator. Dr. Bob Bear is Vice President and Director of Medical Research at St. Michael's Hospital, one of the major downtown teaching hospitals which is associated with the University of Toronto. Let's welcome Dr. Bob Bear to the podium.

DR. BEAR: Thank you very much for the opportunity to come here this morning to address this joint meeting of CLIMOA and AAIM. What I hope to do over the next few minutes is to make some comments relevant to the utilization of the protein/creatinine ratio as a diagnostic or prognostic indicator in the assessment of patients with proteinuria, and then to spend some time talking about microalbuminuria, particularly in patients with insulin-dependent diabetes, but also in patients with other disorders.

I'll begin with this slide. This slide demonstrates someone who is in the state of nervous embarrassment as his luggage is being examined at the airport. It demonstrates the natural history of kidney function impairment progression in patients with a number of different types of underlying glomerular disease. The purpose of my talk here, of course is to try to bring some order out of this chaos and determine if there are some sign posts that can lead us out of the prognostic wilderness. Such sign posts would be of value to me in my clinical life, but of course, would be of extreme importance to you as you assess the risk associated with patients with proteinuria.

Indeed, in persons who are applying for insurance, the presence of proteinuria is always viewed with great alarm. It may indicate underlying serious renal disease and may also be an indicator of other comorbid conditions and potentials for mortality.

What we're really interested in looking at is the urine albumin excretion rate. Normally, each of us would have a urine albumin excretion rate of 5 micrograms per minute or less. Microalbuminuria is characterized by urine albumin excretion rates of 20-200 micrograms per minute. This is not the level of proteinuria that would be easily detected, or detected at all, by the usual dipstick methods or quantitative methods of looking for proteinuria. Classic proteinuria is characterized by excretion rates in excess of 200 micrograms per minute.

There are different ways of assaying for the presence of proteinuria. The one that's been most widely used, in fact is probably continuing to be most widely used in physician's offices, is the dipstick test for proteinuria. A number of prospective studies have demonstrated that the false negative rate associated with this test is 10-20%, and there also may be false positives. And of course, the most common cause of a false negative, less commonly a false positive, would relate to abnormalities induced by the assessment of urines of different concentration. A little bit of protein in a highly dilute urine sample may lead to a false negative test. A false positive test might occur in a highly concentrated urine sample. It really provides virtually no information of quantitative value.

To obtain information of quantitative value, ideally one would proceed to the collection of a 24-hour urine sample. But clearly this type of information is not readily available to those underwriting insurance applications. So protein quantification is sometimes obtained with an on-the-spot sample and expressed as milligrams of protein per deciliter of urine. Again, this leads to the same kinds of difficulties that can be encountered with the dipstick test. Differences in concentration of the urine may give misleading results.
That brings us to the protein/creatinine ratio, which is basically the urine protein concentration expressed in milligrams per deciliter over the urine/creatinine in milligrams per deciliter. The assumption being that over 24 hours the rate of urine protein excretion in individuals with proteinuria and the rate of creatinine excretion will both be constant. If one then determines the ratio, it should be a reflection of activity over a 24-hour period. This ratio can be reduced to the equation of grams of protein over grams of creatinine. The normal value for the protein/creatinine ratio in normal daytime activity should not exceed .15-.2. Now in many of the applications we see in underwriting insurance the value is normally expressed at up to .42. I think that may be a reflection of the fact that there is on occasion some delay in the analysis of these urine samples, and the creatinine may undergo degeneration. Therefore, the denominator in the equation is changing, and the value may be falsely elevated. To encompass this concept, the upper limit of normal for P/C ratio is extended from .2 to .42.

This slide demonstrates that there is, in fact, a reasonably straight line relationship between the protein/creatinine ratio expressed on the vertical axis and the 24-hour urine protein excretion expressed over a standardized body surface area. In fact, one can proceed to calculate an estimated 24-hour urine protein excretion on the basis of a P/C ratio by just taking the P/C ratio and multiplying that by the 24-hour urine creatinine. The 24-hour urine creatinine, however, has to be looked up on tables, because the 24-hour urine creatinine will vary depending upon gender, body size, age, muscle mass, etc. For example, an individual with a P/C ratio of .75 where it's determined that the 24-hour urine creatinine is 1.5 grams, one could estimate an approximate 24-hour urine protein excretion of 1125 milligrams, clearly above the upper limits of normal, which would be 200 milligrams.

The problem with this test is that the creatinine in the urine isn't a constant throughout the 24 hours, but can be effected by diet, by the administration of certain drugs which may impair creatinine excretion, including some commonly used antibiotics, by the technique of laboratory determination of creatinine. The urine protein excretion rate is also not constant throughout the 24 hours. It can be effected by the time of day, by posture, by exercise, and other factors. So one should employ some skepticism in relying overly on a P/C ratio, recognizing that both the numerator and denominator of this equation can be effected by a number of variables. Further, in the literature on this topic, it is suggested that the P/C ratio extrapolated to urine protein values for 24 hours can be useful in separating out patients with orthostatic or benign proteinuria from patients with tubular proteinuria, who are likely to have proteinuria of several hundred milligrams per day, from patients with more significant, more dangerous glomerular proteinuria. Again, I would urge some caution in this regard. The diagnosis of postural proteinuria or orthostatic proteinuria could be made in a patient or an applicant who has proteinuria of a minimal degree on one occasion which disappears on other occasions, particularly in a first morning urine sample. The differentiation between tubular disease and glomerular disease is really difficult to achieve just on the basis of degree of proteinuria.

In fact, I think it's important to assess these applicants not only in terms of the presence or absence of proteinuria, but also in terms of the other risk factors for the presence of underlying significant kidney disease. I'll just provide a couple of clinical examples. What do I mean by renal risk factor profiling? When I see an application from an individual who has proteinuria or in whom I'm concerned about underlying kidney disease, I always consider what's the probable disease? What does the urinalysis look like? Are there casts or not? I consider the degree of proteinuria, kidney function. I think on my list of approximately 10 things blood pressure is in the first five; it's that important in terms of what the prognosis is likely to be. Other things are the duration of follow-up, the age-associated diseases.

Let me provide some examples. Here is an individual who is 30 years old who has lupus and quite minimal, though abnormal, proteinuria. If one looks at renal risk profiling, one could see that just the nature of the disease and the possible abnormal kidney of a creatinine of 1.1 in a young woman, and the fact that there hasn't been a long period of follow-up would make one very skeptical about the underwriting risk here, irrespective of the degree of proteinuria.

This individual has very heavy proteinuria. Again, one can assess risk on that basis, also on the basis of what the probable underlying disease is and whether there are associated diseases, in this instance, the profound hypercholesterolemia that accompanies proteinuria.

This individual has very minimal proteinuria; the P/C ratio here would probably be quite within the accepted range, but there are many red blood cells in the urine. The combination of hematuria and even minimal proteinuria should point to the probable presence of underlying glomerular disease. Even with a normal P/C ratio one would look at this applicant quite skeptically and probably defer initial insurance application and reassess the individual after a period of time.
So in summary, in terms of proteinuria and the P/C ratio it is a useful assay. It can be extrapolated to an approximate 24 hour urine protein value. There are some variables that can effect both the protein and the creatinine excretion rate. It should not be used in isolation, but rather there are other factors such as described that should be taken into consideration in assessing overall applicant risk.

I'll proceed now to a brief discussion of microalbuminuria, initially focusing on microalbuminuria in insulin-dependent diabetes and then making some brief comments on microalbuminuria in non-insulin-dependent diabetes and in non-diabetic disease.

Insulin-dependent diabetes is an interesting disorder. It is a very common disorder. Despite its frequency, however, it has tremendous differences in prevalence from country to country for reasons that aren't clear. There would seem to be an epidemic of insulin-dependent diabetes. If one looks at the disease acquisition rate among young people, it's probably about three times what is was three or four decades ago. There is something unusual happening in terms of the epidemiology of insulin-dependent diabetes.

This is a serious disorder. If one looks at this slide, which addresses the natural history and mortality of insulin-dependent diabetes, one can see that the mortality rates increase markedly in proportion to the age of onset of the disease. In other words, the longer the person has been at risk the greater will be the mortality.

Up until a few years ago, this was considered the natural history of insulin-dependent diabetes in terms of its complications, specifically kidney complications. After an asymptomatic period, which may be characterized by an actual increase in kidney function, 15-18 years following insulin dependency the individual would develop hypertension, then microalbuminuria, then proteinuria, then heavy proteinuria, then kidney function impairment, proceeding to dialysis, transplantation, and death. It was felt up until perhaps ten years ago that this was the history in insulin-dependent diabetics. All of these patients would end up with kidney filters and would proceed to end stage renal failure, requiring dialysis, and in some cases proceeding to kidney transplantation.

It's become apparent, however, over the last 10-15 years that this natural history of insulin-dependent diabetes is, in fact, a mistake in proper representation of reality. As epidemiologists have looked at patients with insulin-dependent diabetes, it becomes apparent that only 30-40% of patients with long term insulin dependence will develop diabetic renal disease. As there is an association between diabetic kidney disease and diabetic cardiovascular disease in general, there are also epidemiologically different natural histories; some patients pursuing very aggressive courses and developing kidney disease and diabetic multi-system disease, and others being relatively protected from that development.

In the ideal world, it would be nice to have a predictive test, clinically, and clearly in terms of assessing these individuals as insurance risks, that would tell the individual reasonably early on in the natural history of this disorder which course was going to be pursued: kidney disease, cardiovascular disease, a progressive downhill course, or a relatively benign course. Some have suggested that the development of microalbuminuria, the excretion of 20-200 micrograms per minute of protein in the urine, values that are detected by the standard dipstick test or quantitative tests for proteinuria, but can be detected by radio immuno assay or other dipstick tests for microalbuminuria. The presence of this abnormality permits one to gain insight into what course the individual is likely to follow. This looks at the development of proteinuria with long-standing insulin-dependent diabetes, just demonstrating that if one looks at incidence and years since diagnosis, the incidence peaks and then falls. This is the kind of curve that's seen in a disease where a certain number of patients, but not all patients, will develop a specific complication. Mogens, in a quite famous landmark article in 1984, looked at 44 patients with long term insulin-dependent diabetics, and he assayed them for the presence of microalbuminuria. Fourteen of those patients had microalbuminuria and 30 did not have microalbuminuria. Then he looked at these patients again after 7-8 years. In the patients who had initially demonstrated microalbuminuria, 12 out of 14 had gone on to develop overt evidence of diabetic kidney disease. None of the 30 patients who did not have initial microalbuminuria went on to develop overt diabetic kidney disease. This is one of the seminal articles suggesting that microalbuminuria may be a differentiating value in terms of the natural history of this disorder.

It's also interesting that when one looked at the blood pressures of the patients in these two groups, while many would have considered all the patients to be normotensive, the patients who had microalbuminuria really had minimally elevated blood pressures, 138 19 systolic over 89 6 diastolic, compared to the individuals who did not have microalbuminuria. This observation has been sustained. The importance of it is that when one sees even trivial elevations in blood pressure in patients with longstanding insulin-dependent diabetes,
that's likely to be correlated with the presence of microalbuminuria. They both begin at about the same time, and as we'll see that has an impact on the natural history of the disorder.

This just looks at the glomerular filtration rate in the patients at the time they were demonstrated to have microalbuminuria, and one can actually see that kidney function at this moment in time in this disease is actually elevated. The glomerular filtration rate in the patients on the left is higher than the patients who did not have microalbuminuria. So assaying kidney function at this point in time would really not be a useful step.

This would seem to be the natural history of disease in people with longstanding insulin-dependent disease and microalbuminuria: there is a long latent period, and then the patients develop IDN (incipient diabetic nephropathy) characterized by microalbuminuria. If nothing is done, that will progress to overt diabetic nephropathy, kidney failure, and ultimately death. Occasionally something can be done, and we'll talk about that in a moment.

This is another slide demonstrating the natural history of diabetic kidney disease in patients with microalbuminuria. At the bottom, you can see the protein excretion patterns. There is a long latent period, the development of microalbuminuria, and then, if nothing is done, it progresses to overt proteinuria. The patient is on a predestined path. The top aspect of the slide looks at kidney function. One can see that in the stages characterized by microalbuminuria, kidney function is often supraphysiologic, or higher than normal.

This just demonstrates that there are kidney morphologic changes that are present when microalbuminuria is first found. This just looks at patients who are normal on the left, patients with microalbuminuria, and then group 3, patients with overt proteinuria. The thickness of the membranes within the glomerular filtering units is progressively increased as one moves from groups one to three, as is the overall surface area of the filtering units. Indeed there are a whole host of underlying pathologic abnormalities and other abnormalities that have been demonstrated to coexist with microalbuminuria in patients with long standing insulin-dependent diabetes, the kidney structural abnormalities that we've described, well-preserved kidney function, more advanced retinopathy, a tendency to high blood pressure, more advanced neuropathy, and very importantly, evidence of increased general vascular damage, suggesting that perhaps microalbuminuria speaks of a generalized process, and a tendency not only to kidney disease, but also to generalized vascular disease. Abnormal lipid profiles, clearly increased mortality.

This looks at the mortality and why patients with long standing insulin-dependent diabetes die. And that of patients who pursue an unfavorable course, over the period of time demonstrated on this slide, a substantial proportion of these patients will die of kidney failure, but an equally substantial proportion will die of coronary artery disease. So the question is, "Is there a relationship between microalbuminuria, not only to the presence of underlying kidney disease, but also to the presence of underlying generalized vascular disease? Is the relationship between microalbuminuria and generalized cardiovascular mortality?" There was a review by Ludvigson from HORN published in On the Risk in the spring of this year. He looked at some of this data, and there is a series of articles suggesting that the presence of microalbuminuria is not only correlated with an adverse kidney prognosis, many-fold increase from diabetic patients without microalbuminuria, but there is also a several-fold increase in the likelihood of death from coronary artery disease and from other cardiovascular diseases if microalbuminuria is present in that patient cohort follow-up.

What are the implications concerning treatment and prognosis of microalbuminuria and insulin-dependent diabetes? I'll just further complicate your underwriting lives for just a moment by indicating that there are some discrete pathophysiologic abnormalities that go on in the kidneys of patients with insulin-dependent diabetes. If this is a stylized nephron or glomerulus, the pressure within this glomerulus in patients with early diabetic kidney disease is increased. That increase in pressure is correlated to the presence of microalbuminuria.

Why does this make your underwriting lives difficult but patient outcome better? It's now been demonstrated that this natural history can be favorably influenced by aggressive blood pressure lowering treatment. This slide demonstrates reductions in proteinuria in patients whose blood pressures have been brought under control. This demonstrates the progression kidney function impairment following the initiation of aggressive antihypertensive treatment. While microalbuminuria is clearly an important prognostic factor in terms of both kidney disease and vascular disease generally, it's also fair to say that when microalbuminuria is detected early, patients are intensively treated with antihypertensive treatment and dietary protein restriction, and one often sees dramatic reversals in the degree of proteinuria, and stabilization of kidney function. So the issue of prognosis is a bit of a moving target at the present moment.
I'll just close by making some brief comments about microalbuminuria in other disorders. In non-insulin-dependent diabetes, microalbuminuria is often found at the time of diagnosis, but then often disappears with initiation of treatment. So there may be something about hyperglycemia itself that may cause transient microalbuminuria. Over a period of time, however, approximately 15% of patients with non-insulin-dependent diabetes will develop microalbuminuria, and in fact, microalbuminuria in patients with non-insulin-dependent diabetes seems to be an extraordinarily important prognostic factor. Cardiovascular mortality will be increased several-fold in patients with non-insulin-dependent diabetes and microalbuminuria. That cardiovascular mortality is not likely to be delayed. It is likely to occur within the first 3-5 years following the development of microalbuminuria. Again, raising the issue whether microalbuminuria is a reflection of a generalized vascular process.

In terms of other disorders, microalbuminuria is beginning to be looked at as an indication of end organ damage in hypertension. The data on hypertensives is too early to discuss in terms of the use of this test as a prognostic measure; it is being used therapeutically, and it's been demonstrated that patients with microalbuminuria and hypertension, as in diabetics, that microalbuminuria may revert with aggressive blood pressure control.

If one looks at the standard population, however, particularly the aged population, the presence of microalbuminuria is an important independent risk factor for mortality. This looks at the presence of microalbuminuria in diabetics and nondiabetics. One can see significant increases over expected rates of peripheral vascular disease, coronary disease, other general morbidities and mortalities over what is expected for that age. This is a study looking at diabetics and nondiabetics with microalbuminuria between the ages of 60-74. Over the period of follow-up there was a reasonably close correlation between increasing degrees of microalbuminuria and increased mortality. That study corrected for other risk factors, such as hypertension.

In conclusion, microalbuminuria is clearly an important prognostic factor in insulin-dependent diabetes. It permits one to tell early on in the individual's course whether the individual is likely to pursue the progressive downhill course, characterized by kidney disease and cardiac disease, or a relatively benign course. It's also a test that's under increased scrutiny in non-insulin-dependent diabetes and hypertension as a general assay of underlying health in the aged. The data here are suggestive of its utility, but the data are less clear than in insulin-dependent diabetes.

DR. ROWAT: Thank you, Bob. This paper is now open for discussion.

DR. MARJORIE KEYMER, Imperial Life Assurance: Thank you very much for your very concise evaluation of both proteinuria and albuminuria. You mentioned the predictive value of microalbuminuria with insulin-dependent diabetics with respect to nephropathy and cardiovascular disease. Can one assume, then, if someone has progressed 20 or 25 years into their insulin-dependent diabetic "career" that in the absence of microalbuminuria they also do not have cardiovascular risk? I'm quite happy to accept that they don't have as much nephropathy risk, but I'm a little more leery about their cardiovascular risk.

DR. BEAR: A general comment relative to that would be that if one looks at long term insulin-dependent diabetics without microalbuminuria, their overall risk of mortality from coronary artery disease is going to be three to four times higher than the standard population. If you look at long term insulin-dependent diabetics with microalbuminuria, their mortality from coronary disease is going to be eight or nine times elevated over the standard population. So clearly there is an increased risk in both groups, but a particularly high risk in the individuals with microalbuminuria.

DR. KEYMER: So the risk basically falls down to that of a diabetic general population.

DR. BEAR: Exactly.

DR. JUDITH BEAMISH, Munich Reinsurance: I wonder if you could comment about proteinuria in the severely obese population. How common is it, and how significant is it?

DR. BEAR: I've seen some papers where the authors have attempted to establish a correlation between even very heavy proteinuria, nephrotic range proteinuria, and morbid obesity. The relationships are rather tenuous. They're characterized by heavy proteinuria in such patients which disappears when the individuals lose substantial amounts of weight. Kidney biopsies have been done under these circumstances and on occasion have demonstrated focal sclerosing and glomerular nephritis, a particular form of kidney disease. So my view on this is that it may be that specific glomerular disease of a significant nature can accompany morbid obesity. Beyond that, on the basis of the information I have, I'm reluctant to comment on the relationship.
DR. BEAMISH: My own observation, anecdotally, is that all the applicants I see who have morbid obesity have proteinuria. What I wonder is that is the risk just related to their morbid obesity; is that the only risk I’m dealing with? Is that already incorporating the risk of proteinuria, or is there an additional risk in the people that are being sent to a reinsurer because they have proteinuria in addition?

DR. BEAR: Again, it’s an excellent question and the scientist in me recognizes this as a complex problem, because those with morbid obesity are more likely to be hypertensive, are more likely to have syndromes of insulin resistance that are correlated with generalized vascular disease, and therefore, for a number of other reasons are more likely to have microalbuminuria or proteinuria. I see this as part of the overall risk of morbid obesity. I’m just reluctant to ascribe this to a specific form of kidney disease that may be related to that.

DR. BOB PAMPE, Munich Reinsurance: At what point in the course of insulin-dependent diabetes would you feel comfortable in saying there’s no microalbuminuria, none is going to develop, this person is not going to go ahead and get diabetic nephropathy?

DR. BEAR: I think that’s a very good question also. Typically, microalbuminuria will begin to develop 15-20 years after insulin dependence in an insulin-dependent diabetic. So if I saw an applicant who had insulin-dependent diabetes for 20 years with no microalbuminuria, I would feel reasonably comfortable about the likelihood of developing kidney failure. I’d still have a high discomfort level about the likelihood of generalized vascular disease or coronary disease in that applicant.

DR. HARRY KELSO, American National Insurance: Would you care to comment on how to interpret the microalbuminuria in light of the concentration of the urine?

DR. BEAR: Most of the assays that I know of for microalbuminuria really haven’t taken that into account. There are some studies that have tried to determine if there was some additional value in doing a microalbumin/creatinine ratio, which would correct for abnormalities in urine concentration. Those studies were reviewed in the On the Risk issue in the spring of this year. My recollection of the studies is that they did not demonstrate a concrete advantage over just the qualitative assessment for microalbuminuria. It’s not uncommon for microalbuminuria to come and go in individual patients. That’s a reflection, probably, of differences in urine concentration. So there are some false negatives in this test. The American Diabetes Association recommends all diabetics with insulin-dependent diabetes who have had the disorder for more than five years be tested yearly for microalbuminuria. Also, testing ideally would occur at the same time of day, first morning urine sample in all patients. That’s less likely to be confounded by the presence of dilute urine.