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INTERNATIONAL FORUM ON ULCERATIVE COLITIS
RISK SELECTION ASPECTS OF ULCERATIVE COLITIS

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DR. PERMAN: Ladies and gentlemen, I'm told that Chicago time is exactly 1:30. So I wish you all a very warm welcome to this fifth international forum. Can you hear me all over the place? Good.

We have a subject which we all find interesting and important and sometimes difficult and a subject that is sort of changing character. We have, I'm happy to say, so far the largest registered audience for this type of forum which means we had to do away with the tables in this room because otherwise you would have been a little too far away for good participation in what we hope will be a good discussion.

We have a very good panel for you which is also a little bit larger than has been before. I would like to start by having the panel members just identify themselves and where they are active and so forth. Can I start with you, Stephen?

DR. HANAUER: My name is Steve Hanauer. I'm a gastroenterologist at the University of Chicago here.

DR. SZELESS: I am Stefan Szeless. I'm the medical director of Generali Austria in Vienna for over more than 15 years. Generali Austria is a member of the Generali Group which is a worldwide operating insurance company.

The company has developed to the east as well as to the west, so we do have members of the Generali Group here in the USA; that is, the BMA in Kansas City. Generali Holding in Vienna is responsible for Central Europe, Austria, Germany and also the Netherlands, but recently since the fall of the Iron Curtain, especially to the East European, the former Communist countries like Hungary and the Czech Republic. Further interests will be the other Eastern European countries. Our strategic field comprises life, health and accident insurance.

DR. PERMAN: Thank you, Dr. Szeless. Obviously we are extending the territory here.

DR. INOUE: My name is Kimitoshi Inoue and I come from Japan. I am not good at English and I'm sorry. I will do my best.

DR. MUTS: I'm Stetske Muts from the Netherlands. I'm working for the National Insurance Company which is the biggest company in the Netherlands for 50 percent of my time and the other 50 percent I'm consultant in the Municipal Hospital.

DR. PERMAN: I should add, I'm Einar Perman. I'm from Stockholm, Sweden. I work with Treconsa Insurance Company there. Last year it was called Treconsa SPP because Treconsa was engaged to SPP but there was no marriage, the engagement broke up.

DR. RAHN: I'm Dr. Shelley Rahn and I work with Mass Mutual in Springfield, Massachusetts.

DR. PERMAN: I have had a lot of correspondence and faxes with Dr. Rahn but in my younger days there was a standup comedian called Shelley Berman, obviously a man, so I always thought it would be a man I was having on the panel. I'm delighted that that is not the case. I understand we are now politically correct.

Let me just give a few of the house rules that might make things easier. I have made up the four cases. The medical directors here have seen them and sort of made their comments and are going to present them to you and they have made their comments to me but I have not disclosed what one thinks to the rest of the audience.

The time plan is that Dr. Hanauer will first give an overview of ulcerative colitis. Obviously we focus on its prognosis which is what concerns us as medical directors and after that, the medical directors in turn, as they sit, will give some 15 minute presentations of how they view these cases from their respective viewpoints and how they evaluate their risks. There will be a ten minute intermission about one hour from now, and then at the end I hope we will have some 20 minutes or so for a general discussion. You're all welcome to comment after each presentation with some shorter questions. If a big issue comes up I'd like to defer it to the general discussion.

I also have to say there is one word that we are not really allowed to use and that is rating and how we should rate. I've just said it to show that it's forbidden. It's really silly because there is no right answer to this that applies to the whole world. I'm sure this disease is in different phases in different parts of the world. Also the purpose of this is not to form any consensus. There is no right answer. There are points of view here and points of view there depending on how the disease presents itself.

In fact, if we do start talking like that, we will be breaking the laws of this country. The panel will be promptly taken in by

some Chicago policemen that are very solid people, or the FBI will be after us or even worse, we will disappoint our ex-President Bill Baker who so kindly has facilitated this whole thing.

May I also say that a transcript is being made of what the panel says and also that means I may repeat some of your questions or most of your questions so that they come into the transcript and then a summary overview will come into the *Journal of Insurance Medicine* at the request of Dr. Elder.

I should also say that if you are in this country you apparently have something called a credit system of which I'm not familiar at all, but there is a book that you should sign at the end of the session and I will see that it gets to the right person. If anyone needs an extra copy of the cases, I have them here.

Dr. Hanauer, you have the floor.

DR. HANAUER: Thank you very much. I want to welcome you all to my city. I hope you have a good stay. Along the lines of what you were mentioning regarding the Chicago police, there is a movie which is now showing in the United States called Barcelona. It's the story of two young Americans who are in Barcelona in the early 1960s when Spain was considering whether or not to join NATO and it shows many of the political conflicts at the time, but there is a wonderful scene where these two young men are dating some Spanish women and to point out some of the ironies, the Spanish women say that America is a very violent society. And the young man says, "What do you mean we're a violent society?" She says, "Well, what about all the shooting deaths?" The young man says, "That does not mean that we're more violent, it means we have better aim." The Chicago police have good aim.

I think I'm going to dispel some myths regarding the morbidity and mortality of ulcerative colitis and I hope to enlighten you on some of the more recent data regarding this disease. I will hope to quickly provide an overview of the prognosis in a series of slides and I'm going to go fairly quickly through this.

I'm not going to mention classification of inflammatory bowel disease in this audience but I will be happy to discuss differences between ulcerative colitis and Crohn's disease. I will only point out some epidemiologic features of this illness that may have some interest to the insurance industry. I will focus on complications, prognostic aspects, mortality and cancer data.

Of interest, ulcerative colitis and also Crohn's disease are diseases of the modern highly sanitized world. It's more common in Europe and in North America and in South Africa, in the cities, Australia and New Zealand.

There is an inverse correlation with ulcerative colitis and Crohn's disease with sanitation. In areas where the sanitation is poor, it's actually a direct correlation. Where sanitation is poor there is a low incidence of disease. Where sanitation is good, there's a higher incidence. It is just on the rise, these illnesses, in Japan.

Whether or not we want to blame the western diet remains a point of controversy. In the United States, I should mention, that incidence is approximately five cases per 100,000 and the prevalence about 50 per 100,000 for both ulcerative colitis and Crohn's disease individually, so you double that for the two.

There is one unique epidemiologic feature and differentiation between these two types of inflammatory disease and that is the history of cigarette smoking. Probably one of the few good things that smoking does is protect against the development of ulcerative colitis, yet it is highly associated with Crohn's disease.

I'm showing you here the risk ratio, the relative risks, for Crohn's disease which is increased in smokers and diminished in ulcerative colitis. About 80 percent of patients with ulcerative colitis are non-smokers and compared to the general population in different countries the smoking rate is lower in ulcerative colitis patients. Interestingly when patients stop smoking, they will often develop ulcerative colitis within a few years. That's in the predisposed population.

As I mentioned, it's the opposite for Crohn's disease. There is great and controversy whether patients who have stopped smoking and develop ulcerative colitis should resume smoking because it really does help their disease activity if they do start cigarettes again. Again there's additional controversy whether nicotine is the factor that has palliative effects.

Now, ulcerative colitis is a disease that produces continuous inflammation from the rectum to some proximal portion of the colon and that upper extent is variable in individual patients. Once the upper extent is determined it usually remains there, as I will show you.

This is some most recent data from a large series of ulcerative colitis patients seen at the Cleveland Clinic, a referral center in the United States. Of these patients, as you can see, about 46 percent had disease limited to the rectum and sigmoid, 17 percent below the splenic flexure and about a third of the patients had extensive ulcerative colitis. The disease extent does have some prognostic aspects, as I will show you.

As I mentioned, once this upper border is determined, it tends to remain there. So if a patient presents with ulcerative proctitis, usually that patient will continue to have limited disease throughout the span of their illness or throughout their life span. Approximately ten to 30 percent of patients will extend more proximally through the course of their illness. If they do, it's usually early on in the course.

There are a number of factors that can influence flare ups of ulcerative colitis, including infection, the use of non-steroidal anti-inflammatory drugs which are harmful in all inflammatory bowel diseases, cigarette smoking cessation. There's an impact of pregnancy in about a third of the patients on their disease activity and major stresses can effect the disease activity. We're not talking about daily life stresses. We're talking about major

stresses such as deaths in the family, divorces, loss of their job, can impact on the disease activity.

Now, the prognosis of ulcerative colitis has been evaluated through many decades and I would emphasize that it's important to look at the more recent data regarding ulcerative colitis rather than the past data. Certainly any information preceding the 1960s is going to be inaccurate because of changes in both the medical and surgical approaches.

In a recent series just published in the journal *Gastroenterology* this year, the Danish group has looked at 1,100 patients who have been followed for now up to 25 years. The distribution of the disease is approximately what I showed you from Cleveland with a little more distal disease.

Some of this depends on how one finds the disease, if the upper margin is demarcated by either a colonoscopy or radiography, may cause variations in these series, but it's approximately the same distribution, with about two thirds or more of the patients presenting with left sided disease below the splenic flexure.

What they looked at was a number of aspects, including the number of patients who had active disease versus quiescent disease and those who had undergone surgery. I should emphasize that removal of the colon cures ulcerative colitis and once the colon is removed, virtually all series have shown there is no increased mortality beyond the general age related general population.

At the beginning of the illness, most of the patients present with active disease but as time goes on, there seems to be approximately a similar proportion of patients who have either quiescent inactive disease, versus active disease, versus those colectomized. As far as the level of activity or the percentage of patients who have active disease, after about the first ten years, the majority, about three quarters of the patients will have inactive disease. Many of the patients with continuing activity have thus gone to surgery during that period of time.

Now, as far as the overall, approximately two thirds of the patients will have intermittent disease activity, so that at any one point, about 25 percent of patients will remain inactive during their first ten years of the disease, about 18 percent or 20 percent will have chronic activity, but the majority, two thirds of the patients have intermittent activity which during the most part is quiet, but they will have intermittent flare ups of disease activity.

As far as the number of hospital admissions, both outpatient and inpatient, after about ten years it tends to remain fairly constant with a low number of only a few outpatient visits and rare hospitalizations as time goes on. Most of the patients have the greatest activity and need for medical care early on in the course of their disease. Again, many patients who have had a colectomy are thus eliminated.

There is some interesting data from this series regarding the working capacity of the patients. At the bottom are patients who are able to work full time, the middle are those who have a partial disability and the white at the top, the very small percentage are patients who are permanently disabled from occupation.

Again, this is from the Danish series where all of the patients with ulcerative colitis tend to be referred into this center. So they have good statistics for most of, at least the Copenhagen region. As far as the cumulative probability of maintaining their occupation, you can see that clearly 90 percent or more patients work full time and never lose their ability to work full time.

Now, the two complications that I will discuss of ulcerative colitis are colon cancer and sclerosing cholangitis as pertains to the cases that you will see. It has been recognized for the past 30 years that there is an increased risk of colon cancer in patients with ulcerative colitis compared to the general population.

When we look at that risk in a variety of different series, there seems to be a splay in that risk, with some series showing up to 60 percent of patients at 40 years having been found to have cancer and in others only about 20 percent at 40 years, a major difference. Now, there are probably two reasons for this wide variance.

The first is the referral bias. Many patients with colon cancer within the course of ulcerative colitis have been referred to tertiary centers of expertise and that probably accounts for the upper margin. But on the other hand, we now recognize that the risk of cancer in ulcerative colitis is primarily related to two factors.

The first is the extent to colitis, how much of the colon is involved, and the second is duration. A third factor that seems to be becoming important is that of evidence of liver disease, especially sclerosing cholangitis as our Swedish colleagues have demonstrated. We'll talk about that in a minute.

The risk factors for cancer in ulcerative colitis are mucosal extent. So patients with pancolitis are at greater risk than those with proctitis or proctosigmoiditis, patients who have had disease of increasing duration and as I mentioned, those with primary sclerosing cholangitis.

Another risk factor which is used now to screen patients who are at risk is that of mucosal dysplasia or epithelial dysplasia. Now, there are a number of controversies that I will point out regarding the aspects of cancer surveillance and dysplasia. Dysplasia is cellular atypia which must be differentiated from inflammatory atypia and there have been some standard pathologic criteria for determining the level of dysplasia.

In the past we had differentiated between what was called indefinite dysplasia which was usually associated with active inflammation, low grade dysplasia or high grade dysplasia which is essentially carcinoma insitu. As it will turn out, it's probably not as important to differentiate because if we are using dysplasia as a marker for colonoscopic surveillance, any evidence of

confirmed dysplasia is now being accepted as a criteria for removing the colon and removing the risk for cancer.

Many of the problems with our previous screening programs and the failures of surveillance programs to protect patients against invasive cancer has been that we have waited for the patients to progress from low grade to high grade dysplasia before removing the colons and once patients have high grade dysplasia, there is a 50 percent likelihood that they already have an invasive cancer at that time.

So the marker, the standard for acting in a surveillance program should not be high grade dysplasia, it should be evidence of confirmed low grade dysplasia.

Another risk factor which is associated with the finding of dysplasia are strictures in ulcerative colitis. Unlike Crohn's disease, ulcerative colitis is not a stricturing disease. It is a mucosal process. So although there may be some muscular hyperplasia, permanent or non-reversible strictures in ulcerative colitis are almost always associated with mucosal dysplasia. This is a finding that should be a high suspicion for associated neoplasia.

Currently there have been a number of surveillance procedures that have been looked at, but to date the only one that is currently realistic, colonoscopy and biopsies along the length of the colon, looking for dysplasia. Some of the controversies regarding these cancer surveillance programs have been how we interpret dysplasia, classifying it between pathologists.

In some places it's referred to as mild atypia and that may be by different criteria that have now been standardized. As I mentioned, most of the series have not performed colectomies for low grade dysplasia and we are now finding that many patients with low grade dysplasia are found at their next examination to have cancers. It's a very unpredictable finding.

So if you're going to act, we must act on low grade dysplasia. The failures in the screening programs have often been due to either not acting on low grade dysplasia or patients who fail to come back for their regular screening examinations.

Another problem has been some controversies of whether these screening programs are cost effective. I'm not certain that that really applies to this audience. It's more of a general issue of how to do this in a most cost effective manner and the gastroenterologists are currently sorting this problem out.

We feel, from our institution, and this is data that we will present at next year's American Gastroenterologic Association, that when we have looked at patients who have had a colectomy for whatever reason and we use the colectomy as a gold standard for whether or not there is dysplasia or cancer, that when we look at the previous colonoscopic biopsies we actually have very good negative predictive values for negative examination.

In other words, if a patient is free of cancer or dysplasia, that is a very reassuring test that they are not going to develop cancer in the next screening interval.

Now, the other complication that I will mention briefly is that of liver disease in ulcerative colitis. There is a spectrum of liver disease associated with ulcerative colitis. A biopsy may show what we call pericholangitis. The Mayo Clinic calls this small bile duct cholangitis.

Pericholangitis is asymptomatic and is manifest by minor elevations in the biliary enzymes of the alkaline phosphatase and GGTP without elevation of the transaminase or elevation of bilirubin and usually it is a non-progressive disease. It usually remains asymptomatic through the course, as I will show you.

On the other hand, sclerosing cholangitis is a progressive form of liver disease that eventually develops into a secondary biliary cirrhosis. Sclerosing cholangitis which can be identified either at biopsy or on cholangiogram either via transopatic or ERCP and it must be distinguished from cholangiocarcinoma which is now being recognized as a major complication of long term sclerosing cholangitis.

So just as long duration of ulcerative colitis leads to colon cancer, long duration sclerosing cholangitis leads to cholangiocarcinoma. However, most patients are currently being transplanted before they find cholangiocarcinoma.

Now, a recent publication looking at liver disease in the Stockholm County published by Broome and Gut, looked at 1,200 patients with ulcerative colitis and they found that of these, 11 percent had liver enzyme abnormalities but only about 2.3 percent, less than three percent of the ulcerative colitis patients developed primary sclerosing cholangitis.

The other patients all resolved their liver enzymes or were related to either pericholangitis which would be the active colitis or infection or drug reaction or non-related disease. So the incident of pericholangitis is very small, only about three percent of ulcerative colitis patients. The Mayo Clinic has described this spectrum between pericholangitis and progressing sclerosing cholangitis leading onto to cirrhosis, and they have looked at 174 patients, this is a very large series, that have been referred.

Keep in mind this is a referral population to a tertiary medical center. They divided the patients into those who were asymptomatic versus those who were symptomatic and of course, they had a much higher percentage of patients referred symptomatic because of their tertiary nature. They looked at the risk factors for mortality in this population and they identified the following risk factors by a multi-varied analysis.

Those who were symptomatic at presentation, those who already had fibrosis at biopsy, those who were older and those who had either an elevated bilirubin, diminished hemoglobin or the presence of inflammatory bowel disease. The last is some-

what of a fallacy since now we know that more than 90 percent of patients with sclerosing cholangitis do have ulcerative colitis and those who don't, probably will develop ulcerative colitis at some point.

When they looked at the survival group of the asymptomatic versus symptomatic, those who were asymptomatic had a very good survival. Again keep in mind the asymptomatic patients referred to the Mayo Clinic were the sicker of these patients, they had higher liver enzyme abnormalities. And what they then identified was looking at the number of risk factors, they looked at survival, and again the more risk factors the patient had, the less likely the patients were to go on with long term survival.

Of course, this survival is not interrupted by the intervention of liver transplant in patients with progressive disease. But also please keep in mind that these statistics apply to less than three percent of the ulcerative colitis population.

Now, as far as the mortality in ulcerative colitis, I would urge you to be cautious in looking at the contemporary series versus early series, and also whether or not patients are looked at in community versus a tertiary center to avoid this referral bias. In early series it's been recognized that ulcerative colitis did have a poor prognosis with the first attack, with mortality up to 26 percent with the first attack. This no longer applies.

Patients who were treated prior to steroid therapy, had high surgical complications and if you look at early series versus the later, just before and after 1952, there was three times increased mortality before 1952 versus after. Also about 15 percent mortality in the early series were related to cancer death that hopefully we will be able to intervene.

Some of the early series just showed a relative poor cumulative ten year survival with ulcerative colitis. But again early series occurred only up to the latest in 1984, and in later series, the better the long term prognosis was, compared to the early series with the ten year survival.

A very recent series that was published last year in Digestive Disease and Sciences, looked at a British group of 1,000 patients who were compared to age related patients in the same county and they found the standard mortality ratio was 93, no different from the general age matched population. In the patients who had a colectomy during that time, again there was still no increased mortality compared to the general population. And they found no difference in the standard mortality ratio according to the mucosal extent of disease.

So to summarize this mortality, the mortality after the first attack approximates that of the general public. The risk factors that have been recognized for increased mortality really are only a few. One is non-compliance with the surveillance program, patients who are not going to come back after eight to ten years of disease for regular screening and evidence of progressive primary sclerosing cholangitis. Aside from that the evidence seems to imply that the mortality from ulcerative colitis is otherwise the same as the general population when appropriate age match controls are examined. Thank you.

(Applause.)

DR. PERMAN: Thank you very much, Dr. Hanauer, for a very fine overview. I'm sure this has raised some questions in your mind but I would like to suggest, in the interest of time and focus, that we save these questions for the general discussion. I particularly like the way you really managed to focus on what is important for us, namely prognosis.

I now give the word to Dr. Stefan Szeless.

Cases for discussion

General. These four businessmen all apply for a $600,000 US policy. They are 40 years old and have no medical history except for ulcerative colitis. They work full time, report modest alcohol habits and are non-smokers. No medical impairments except those given in text. Rate each applicant by expressing mortality in percent of standard mortality (standard mortality = 100 percent).

Applicant One. (total colitis, 20 years duration) This applicant developed ulcerative colitis 20 years ago. His colitis involves the whole colon, biopsy findings are consistent with the diagnosis. During the first year his illness was more active. He required steroids during several periods, and was at one time hospitalized for one week because of more pronounced symptoms. Since then he has been on sulfasalazine, and his colitis has been largely inactive. His only symptom has been occasional, short periods with loose bowel movements. Yearly control coloscopies have not shown dysplasia. No laboratory signs of extracolonic manifestations of the disease.

Applicant Two. (left-sided colitis, 20 years duration) This applicant developed ulcerative colitis 20 years ago. His colitis involves only the left colon, biopsy findings are consistent with the diagnosis. During the first year his illness was more active. He required steroids during several periods, and was at one time hospitalized for one week because of more pronounced symptoms. Since then he has been on sulfasalazine, and his colitis has been largely inactive. His only symptom has been occasional, short periods with loose bowel movements. Yearly control coloscopies have not shown dysplasia. No laboratory signs of extracolonic manifestations of the disease.

Applicant Three. (total colitis, five years duration) This applicant developed ulcerative colitis five years ago. His colitis involves the whole colon, biopsy findings are consistent with the diagnosis. During the first year his illness was more active. He required steroids during several periods, and was at one time hospitalized for one week because of more pronounced symptoms. Since then he has been on sulfasalazine, and his colitis has been largely inactive. His only symptom has been occasional,

short periods with loose bowel movements. No laboratory signs of extracolonic manifestations of the disease.

Applicant Four. (total colitis, five years duration, abnormal liver tests) This applicant developed ulcerative colitis five years ago. His colitis involves the whole colon, biopsy findings are consistent with the diagnosis. During the first year his illness was more active. He required steroids during several periods, and was at one time hospitalized for one week because of more pronounced symptoms. Since then he has been on sulfasalazine, and his colitis has been largely inactive. His only symptom has been occasional, short periods with loose bowel movements. During the last year abnormal liver tests have been present with:

	value	normal range
SGOT (aspartate aminotransferase, AST)	55 U/L	0-35
SGPT (alanine aminotransferase, ALT)	55 U/L	0-35
GGT (gamma glutamyl transferase)	45 U/L	0-30
Alkaline phosphatase	200 U/L	30-120
Bilirubin (total)	15 umol/L	2-18

No serum markers for hepatitis B or C. No serum autoantibodies indicating the presence of chronic hepatitis or primary biliary cirrhosis. Ultrasound examination of liver and biliary tract normal. No liver biopsy made.

DR. SZELESS: Dr. Baker, Dr. Perman, ladies and gentlemen, before going to the rating and to the discussion of the four cases, permit me to make a general statement about our situation.

Ulcerative colitis is a rather infrequent impairment in life insurance compared to other illnesses, like hypertension, diabetes or coronary artery disease. I can definitely say that in our company in day to day insurance work, ulcerative colitis is a relatively infrequent occurrence.

As far as I could ascertain from relevant medical literature, there is an obvious north/south gap in the prevalence of the disease which varies between 28 and 117 per 100,000. These numbers should be regarded with caution since unspecific proctitis and colitis is too frequently diagnosed and might be added to the prevalence of ulcerative colitis.

The prevalence of ulcerative colitis in Austria may reach 70 per 100,000 at maximum. This corresponds to a total of about 500,000 to 503,000 cases of ulcerative colitis for the Austrian population of 7.5 million. This figure is roughly the same as given to me by the medical director of a large Viennese hospital which is responsible for more than 100,000 people who said that 0.6 to 0.7 percent of his patients suffer from ulcerative colitis.

If we assume that approximately 40 percent of our population is covered by life insurance with our company, representing about ten percent of the market, we find approximately 200 ulcerative colitis cases in our portfolio. Therefore, it is obviously that I, as chief medical underwriter, observe not more than ten to maximum 15 ulcerative colitis cases per year. I also want to point out that all ulcerative colitis cases, at least in our company, are evaluated only by MDs and not by non-medical underwriters.

Now, I would like to proceed to the ratings of the four cases whereby the first case should be regarded separately. The scenarios one, two and three are quite similar. They have the same age, the diagnosis ulcerative colitis is proven, no surgical treatment, conservative treatment with sulfasalazine, no need for steroids, no complete remission, minimal to mild complaints, yearly coloscopic controls, no dysplasia and no signs of extracolonic manifestations. In medical literature, as well as in our rating manuals, we find positive and negative factors inferencing the prognosis and therefore effecting the mortality of ulcerative colitis.

Let me now illustrate for you these features as reflecting in our cases. We have several features in our cases, like low activity, no or minimal symptoms in all three cases, therapy with sulfasalazine, no need for steroids in all three cases, yearly coloscopy, no dysplasia in all three cases, no laboratory signs of extraintestinal manifestations also in all three cases, left sided ulcerative colitis only in case two, short duration in case three, other features, long duration, risk of malignancy in case one and two, no complete remission in all three cases, diffused complete colitis in case one and three, early onset of disease in case one and two.

Based on the above information, we can assign pluses and minuses to each case. Therefore, in case one total colitis of long duration, 20 years, indicates to me a mortality of plus 100 percent. That's a total of 200 percent. The cases one, two and three differ solely through the duration of disease and the extent of disease. Consequently, when evaluating these scenarios we have to consider two principle questions. First, is there an increased risk for colon cancer resulting from the duration of ulcerative colitis? This question can be answered with a clear yes.

Although cancer risk in ulcerative colitis was previously overestimated during the last decades, as indicated in medical literature, more recent studies still indicate a higher cancer risk with relation to disease duration.

The next overhead shows cancer risk in ulcerative colitis dependent on disease duration. From Greenstein 1979, you see ulcerative colitis, duration 10 years, a cancer incidence of 0.4 percent. Ulcerative colitis, 40 years, increasing to 52.6 percent. From Gyde, 1998, ulcerative colitis after 20 years, 7.2 percent; ulcerative colitis, 30 years, going up to 16.5 percent. Numerous other investigations exist that indicate the same tendency.

The cancer risk of ulcerative colitis increasing duration of the disease correlates to higher incidence of cancer. Studies from Birmingham, Oxford, Stockholm, Cleveland, London and Prague attest to that point. According to the information in case three, with only five years duration of disease, I would rate the cancer risk more favorably than in case one... plus 50 percent.

That's a total of 150 percent. At this point permit me to remark that even in more recent publications, for example, in Denmark I found much more favorable results on cancer risk in ulcerative colitis. In the Copenhagen study there was no higher cancer risk in patients with ulcerative colitis compared to the general mortality rate of the Danish population, 0.6 versus 0.7 percent.

With this remark, I just wanted to point out that there are a lot of contradictions in literature that I reviewed on ulcerative colitis, but if these results will be proved they will have an impact on our daily insurance work when rating these cases and it will be the task of the insurance companies to implement these more favorable mortality rates into our rating manuals and hence, will positively influence our decisions.

The second question posed relating to the three scenarios is, what is the extent of the disease and its influence on cancer risk or referring to our cases, is there a difference in cancer risk between universal and left sided colitis? The answer is cancer in left sided colitis, although less frequent than in universal colitis, still appears to constitute a considerable risk in the third and especially in the fourth decade of disease.

Cancer free survival in universal and left sided ulcerative colitis as a function of duration of colitis: Patients with left sided colitis appear to survive free of cancer about ten years longer than patients with universal colitis. With reference to case two, this indicates to me that with good surveillance, yearly colonscopic controls and disease duration of 20 years, the cancer risk is practically negligible. I would rate it as borderline normal.

And now to case four. In this case the main question is whether primary sclerosing cholangitis exists or not. In order to answer this question, I reviewed a checklist of criteria presented in primary sclerosing cholangitis which comes from the Mayo Clinic, 1990. Features shown in primary sclerosing cholangitis as related to case four to be considered are the sex, ulcerative colitis present in 70 percent, symptoms, signs and laboratory findings. If one applies this checklist to our applicant, then it is obvious that the first three criteria are applicable; however, there are no symptoms or signs that support the existing of primary sclerosing cholangitis, therefore one must resort to laboratory findings.

In our case there are some higher liver parameters but which are not of the magnitude of those presented in the table. So despite the checklist and what I could discover in relevant medical literature, I cannot give you a clear answer whether primary sclerosing cholangitis is present or not. I would recommend to our company to require further investigations, like an ERCP because of three reasons. First, ERCP is the method of choice to diagnose primary sclerosing cholangitis. Second, according to the checklist the criteria for proof of primary sclerosing cholangitis are not fulfilled to a higher degree. And third, insured value is rather high, so an additional test is certainly justified; however, if I must make a decision without the benefit of an ERCP then I would decline the case considering the fact that primary sclerosing cholangitis is associated with chronic ulcerative colitis in 70 percent of patients as also illustrated in the overhead.

For me personally, this fact is the greatest pro-argument that primary sclerosing cholangitis might be present. At this point, we recognize certain problems in this case. For example, can one determine a threshold in laboratory tests at which the existence of primary sclerosing cholangitis is seriously to be considered. Or how do we proceed when the applicant is not subjected to thorough medical surveillance like yearly coloscopy, etc. Perhaps these and other open questions can be answered by the specialists present or in the ensuing discussion. Thank you.

(Applause.)

DR. PERMAN: Thank you very much, Stefan. Are there any direct short questions in connection with this presentation? If not, I suggest that I give the word to Dr. Kimitoshi Inoue.

DR. INOUE: Thank you. Stefan talked about everything. I have nothing to talk about on these cases, but I must speak. It is a pleasure for me to be here as part of this international forum and I thank the director of the organizing committee for inviting me.

I will submit my rating of present cases mainly on rising Japanese clinical data on mortality because every country it's all medical problems. Before talking to you about the rating on the applicants, I would like to tell you three interesting backgrounds about ulcerative colitis in Japan.

The incident ratio per 100,000 for 1955 through 1985 is known. The incidence rate is under one per 100,000 before 1965 but it increased to over four per 100,000 in 1975. From 1975 to now it is almost three per 100,000.

Onset rate of ulcerative colitis is greatest at age 20 to 24 and nearly as great at age 15 to 19. I don't know the reason for the sudden increase in ulcerative colitis but interesting phenomena of social behavior, especially diet, occurred in Japan from 1950 to now. If the ratio of animal protein compared with total intake protein is high, most of the protein is from animal protein. There were changes in lifestyle, especially diet in Japan, according to figures by the ministry of health inspection report about nutrition. Initially the way it has been from 1950 to 1962. The second wave happened from 1963 to 1967. It is a decrease of consuming rice, a result of people's movement from rural areas to cities.

Something happened from 1968 to 1973. It is a sudden increase of eating animal protein. I remember when I was in school, my mother every morning talked to me, "Why don't you eat two eggs?" I would eat just one egg and my mother would talk to me. The next wave happened in 1974 to 1977 because the disruption in the Japanese oil supply. During the resulting recession there was much discussion if animal protein was really so good.

The fifth wave is a questioning of the new lifestyle and diet. People hope for a new healthy life but wonder if the new Japa-

nese lifestyle is truly healthy or not and just wondering until now. We know that a sudden increase of animal protein intake corresponds to the increase of ulcerative colitis in Japan.

It is interesting that the increase of ulcerative colitis corresponds to the increased animal protein intake. This shows that an increase of animal protein intake after a decrease of consuming rice might be one of the reasons to introduce ulcerative colitis in Japan. It is possible that the change of diet might stimulate the immune response to the colon in Japan. It is true that change of society and culture reflects the disease.

The second phenomenon makes a point for underwriting the case of ulcerative colitis. The rate of colon cancer as a complication of ulcerative colitis is fortunately lower than in other countries. 30 percent afflicted, 0.3 percent in Japan according to Fukushima, 1990. We must consider its influence upon the mortality ratio of ulcerative colitis. The morbidity of ulcerative colitis in 1987 is 5.68 per 100,000 in Japan according to Utunomiya in 1988. Now, I will talk about my basis of rating in Japan.

This is a study done at Tohoku University School of Medicine. I show cases of ulcerative colitis which required hospitalization. Out of 221 cases, 15 concluding in death. It is a small study but the data is correct. It represents the best study of hospitalized patients of ulcerative colitis in Japan. This line represents the mortality ratio. The applicant who has a past history of ulcerative colitis requiring hospitalization should be denied within three years over 50, according to this study by Hiwatari, et al.

Let's start with applicant number two because this is a more serious type of ulcerative colitis. Applicant number two, I don't have data beyond 11 years. My mortality ratio of ulcerative colitis is just over 95 after 11 years. Anyway I must underwrite this case. My data shows that a mortality ratio will be decreasing over 11 years if there is no complication of colon cancer.

In Japan a patient doesn't take treatment over 20 years if he is recovered. Applicant number two is still taking sulfasalazine and having occasionally trouble with the colon. It shows that he recovered completely and inflammation has still continued. So my rating is plus 100. At the time I assume little complication of colon cancer in Japan; however, ten years in the future we may underwrite more strictly as more cases of long duration may increase the incidence of cancer.

Applicant number one is more severe than number two. We must add plus 100 to number two. I don't exactly have data. My rating is plus 200. Applicant number three, my rating is plus 225 according to hospital data. This is the last case, applicant number four, inflammation is still strong in this case and so my rating has decline. I'm afraid that my rating is not the same as other panelists. There is a reason for this as you have seen by the overhead projections. Ulcerative colitis is not seen in Japan as frequently as in the United States and Europe, the morbidity being only 1.3 as great, possibly because of historical differences in culture, genetics, diet. Ulcerative colitis is only being seen with any frequency in Japan.

It is suddenly possible that we may see more incidence of long term ulcerative colitis and an accompanying increase in colon cancer. Thank you for your patience.

(Applause.)

DR. PERMAN: Thank you, Dr. Inoue, for your fine presentation. You certainly shouldn't have any feelings about your ratings possibly differing from others because that's what this forum is about and who knows, there are reasons why the disease may have a different profile in your country. Any questions for Dr. Inoue?

Well, if not, if you come on them, save them for the general discussion. We will now take a ten minute break, and there are some refreshments at the other end of the room.

(A recess was taken.)

DR. PERMAN: Dr. Muts-Homsma, you have the floor.

DR. MUTS-HOMSMA: Good afternoon, ladies and gentlemen. With the preparation of my rating, I concentrated primarily on the development of carcinoma because I thought that is most important in these case histories.

All applicants are on sulfasalazine therapy which seems to be rather beneficial concerning the development of carcinoma. They're all known smokers. Regarding smoking or non-smoking, smoking seems to be beneficial for ulcerative colitis but I leave that point because as far as I know, no prospective trial has been done concerning the relation between smoking and non-smoking with the development of carcinoma.

On the other hand, in the Netherlands, we do not calculate an extra premium for smoking and we don't do a reduction for non-smoking, so I leave that. There was no medical history except the ulcerative colitis. There are some advantages and some disadvantages. There were some, as I said already, on sulfasalazine therapy. In the Netherlands most patients do not have sulfasalazine any more. But we think that makes no difference. Then the yearly colonoscopy, that's rather much.

I live in a wealthy country and our health care system is well organized. But I don't think a yearly colonoscopy is performed in a patient who has an inactive disease in the Netherlands because it's quite expensive and an uncomfortable examination and I don't think patients are willing enough to go and be two days out of work. Another advantage noticed is dysplasia at biopsy. I'll come to that later on.

Applicant one and three have total colitis and that is a more serious question concerning the development of carcinoma. They have long standing disease, 20 years duration which means overall, what I read from the literature, a cumulative cancer risk of

seven percent which is a substantial risk. In active disease, I read it may be a disadvantage because patients with an active disease are more willing to undergo investigations or need investigations that you do biopsies.

Concerning colonoscopy, as I told you already, an uncomfortable investigation but that's not a point of major concern. The association of dysplasia, cancer might be conflicting but as I heard, a first degree of dysplasia implies that you have to remove the colon. Another important point, multiple biopsies sampled much less than one percent of the surface area of the colon. I think that's important. You have to take into account there might be sampling errors.

Although you perform a good colonoscopy, nicely done and you have taken biopsies, you can insert this specific point. There is a survival benefit, so you have to do it. You will find Dukes A or Dukes B cancer rather than Dukes C.

Could we rely on it? There's not a prospective randomized trial done and I think it's not ethical because you cannot put in patients in one branch and do not perform a colonoscopy. I think you cannot withhold that investigation. Cancer in colitis is part of the long term care of a chronic disease. I think that is important for us. We are working in live insurance and we have to think about long term care. Avoidance of a colectomy is important to maintenance of life and health.

Then I come to my ratings. Applicant one, ulcerative colitis, 20 years, total colitis, not entirely in remission. He has some uncomfortable bowel movements. Yearly colonoscopy done without dysplasia. I think mortality is 200 percent which means plus 100 percent for this applicant because in long standing disease there is a substantial risk for the development of carcinoma. A yearly colonoscopy is done, but as I said, you have to deal with sampling errors.

Applicant two, left sided colitis, less severe disease but a long standing disease, a substantial risk for development of carcinoma. I think less mortality, plus 75 percent.

Applicant three, colitis for five years, not entirely in remission. In the Netherlands most policies end up at the age of 60 or 65, so I don't have to be afraid of a carcinoma with this applicant but he has only had his illness for five years. He can develop sclerosing cholangitis. I think there is a higher mortality, plus 100. In this case I would suggest, for myself, to make reassessments after five years. If he is still inactive then I would say I give him a lower mortality.

Applicant four, a most serious case. Ulcerative colitis for five years, not entirely in remission. Last year he proved to have abnormal liver function tests and he is under suspicion of sclerosing cholangitis.

I think we know too little about this applicant. We have only one series of liver functions tests and I think we need another series. I would postpone until second lab results are available. If he has progressive liver disease, then I would refer him to his physician. He needs maybe an ERCP which seems to be the gold standard for establishing the diagnosis, and eventually a liver biopsy. Thereafter, if he is proven to have sclerosing cholangitis and he still asks for his insurance, then I don't know. I have to calculate very high mortality because I think the survival rate is rather low.

After eight years survival was 80 percent which means 20 percent are deaths, and that is rather high compared to a normal healthy adult of 40 years old. In my situation I will give it reassurance and I will ask the medical advisor what he will do.

(Applause.)

DR. PERMAN: Thank you, Dr. Muts-Homsma, a fine presentation also giving a little bit of the applicant's view of things. Dr. Rahn, you have the floor.

DR. RAHN: As Dr. Pokorski said to me before, he said, being the fourth speaker, do you have anything new to add to this conversation? And I said, well, it's going to be tough but some of it will be repetitive and you'll have to bear with me a little bit.

In an effort to determine the mortality ratio rating for the four cases presented, I will review some of the studies available.

Mortality in ulcerative colitis, as you've heard, is derived from both the short term complications of the acute disease as well as the long term complications of chronic disease. Complications, which we don't have to deal with in these situations, include toxic megacolon and perforation and transfusion requirements, etcetera, and urgent surgery.

This usually arises in the first few years of the disease or in those individuals with severe persistent symptoms. As I said, in these cases, these situations don't arise, therefore I'll concentrate my conversation on the long term chronic complications of the disease, those including obviously colon carcinoma and sclerosing cholangitis.

It is well known, as has been stated already, that the risk of developing colon carcinoma rises with the time from the diagnosis of ulcerative colitis and the length of that involvement. The risk of carcinoma specifically begins to rise in approximately the eighth year after the onset of the disease. The age of onset, as an independent factor, does not seem to effect the risk of developing colon carcinoma.

Cumulative rate of colorectal cancer development has been controversial, as we've also been informed, the rates ranging from as high as 60 percent over 30 years in the referral base population to as low as 1.4 percent over 18 years in another more community based study.

I'm trying to look at the middle ground of a community based gastroenterologist, Dr. Catscomb in Long Island, proposed that there was a rate of approximately 12 percent incidence of colorectal cancer at a 26 year time frame from the onset of disease. Another way of looking at the risk of developing cancer would be the annual rate. This relative cumulative risk is estimated to be anywhere from a half to one percent per year after the tenth year of disease. Thus, someone with a disease for 20 years would have a cumulative risk of anywhere between five and ten percent.

The relative cumulative risk of colon carcinoma compared to the general population has been estimated to be anywhere from a five to a 30-fold increase, obviously from an insurance perspective, a significant risk. Translating this data into mortality ratio is equally as confusing and difficult. The studies available are quite new and present variables that make their utilization difficult. The largest mortality study available is the medical impairment study. This study looked at approximately 10,000 policies on individuals with ulcerative colitis at the time of their issue. The issue date of those policies were dated from 1952 to 1976, and the experience ranged from ten to 24 years from the date of issuance.

One of the problems with that study is obviously the earlier cases, the ones that we would be interested in from a long term perspective were the ones that therapies were not quite as good as they are today, so therefore the data are very confusing and hard to interpret.

The mortality ratio in that study on the combined standard and sub-standard issued policies for a 40 to 49-year-old age was determined to be 117 percent. That's not taking into account that's all commerce. The mortality ratio for the 15 to 39-year-old age group was 251 percent. Assuming that the decreasing mortality ratio with age is linear, which may be a leap of faith, the mortality ratio on a 40-year-old would be approximately 150 percent. Those individuals when looking at the group as a whole, all ages, with 16 to 25 year duration of the disease, had a mortality ratio of only 128 percent.

The limitation of this study was that when the data were analyzed with regards to those issued sub-standard, it's not quite clear what made certain people sub-standard versus standard. Those issued at sub-standard rates, the mortality ratio was higher and for the standard rates, that was a rate of 260 percent. In another non-insurance study, overall age and sex specific mortality is estimated to be approximately 200 percent.

So when reviewing the cases presented, several interesting comparisons can be made with regard to mortality. Of significance is the comparison of the mortality associated with universal colitis of 20 years duration versus five duration; i.e., cases number one and three respectively. Specifically with regard to the cases number one and three, one individual developed ulcerative colitis at age 20 and has had his disease for 20 years. The other developed universal colitis at 35 and has had his disease for only five years.

On initial review it would seem that applicant number one would have a much higher mortality risk than applicant number three based on the duration of disease. However, applicant three is still young from a life insurance age perspective. The individual with 20 years of the disease in my estimation has an approximate 200 percent risk compared to the general population or the general insurance population, based on the medical impairment studies and some of the other information I presented.

Extrapolating backwards, the individual with five years duration of the disease intuitively should have a low mortality risk compared to the applicant with 20 years of disease, assuming that his cancer risk will not be as evident until he's closer to age 55 where he would be more closely matched with his age group in terms of the risk of colon cancer. This individual in my estimate would have a mortality ratio of about 150 to 175 percent.

The case presentations mentioned surveillance for dysplasia. The benefits of surveillance has been widely disputed with regards to detecting cancer at an earlier age, at a more treatable stage in regards to mortality. At best it is an imperfect method but the indication that an applicant has had yearly colonoscopy performed is evidence of close follow up. Optimistically that level of care may improve an individual's mortality. Applicant number one has demonstrated compliance, whereas applicant number two's level of future compliance regards to surveillance is unknown.

This information also narrows the rating between these two individuals. Another interesting comparison is the difference between left sided colitis and universal colitis of similar duration. Applicants number one and number two have both had their disease for 20 years but number one has pancolitis, number two has left sided disease. An increased risk of colorectal carcinoma in left sided disease compared to the standard population has been established.

This risk, however, appears to be less than in pancolitis and it has been suggested it occurs a decade later than in universal colitis; i.e., the risk begins to increase in approximately the 18th year of disease. I would therefore assume the mortality risk of applicant number two to be significantly less than for number one, and it is my opinion that applicant number two's mortality risk would be approximately 125 to 150 percent.

The last case raises the question of finding of abnormal ALTs in someone with ulcerative colitis. This is not an uncommon finding, as we've heard. Approximately ten percent of all patients with inflammatory bowel disease have some biliary involvement. Associated findings include a vast range of diseases, including pericholangitis, fatty liver, chronic hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis. Hereafter referred to as PSC. PSC is one of the most significant biliary diseases associated with ulcerative colitis from a mortality perspective and is estimated to occur in anywhere from one to four percent of patients with ulcerative colitis.

The diagnosis is highly suspected where there is an elevation of alkaline phosphatase and GGTP. The diagnosis of PSC is best made on ERCP or on liver biopsy. The prognosis for patients with PSC is quite poor, from the onset of symptoms which average two from the onset of the disease. Survival averages only approximately six years after the onset of symptoms. Unfortunately in eight to ten years of survival rate in a 40-year-old the mortality is greater than can be accepted for life insurance.

Applicant number four has had some workup for his abnormal ALT's eliminating many of the possible etiologies, but without any RCP and no liver biopsy, PSC in my opinion still remains a distinct possibility. In conclusion by index of suspicion and mortality ratio of PSC is high enough that I would decline applicant number four until he had further workup.

(Applause.)

DR. PERMAN: Thank you, Dr. Rahn. Are there any direct questions to Dr. Muts-Homsma or Dr. Rahn?

AUDIENCE MEMBER: Dr. Rahn, could I ask you to repeat your ratings?

DR. RAHN: This is the mortality ratio in total. Number one was 200, number two was 150 to 175, number three was 125 to 150 and number four was declined.

DR. PERMAN: Just to repeat, it was to clarify the ratings, Dr. Rahn's ratings. A question from Dr. Pokorski. Just for the record. Do we have any other questions before we start the discussion? If so, may I make the suggestion that I show you on the overhead the combined, how every case was rated by the four medical directors and also may I suggest that Dr. Hanauer gives his impressions of this evaluation of risk. Can I please have this one shown here and Dr. Hanauer is the only one who has seen this before, so please, Dr. Hanauer.

DR. HANAUER: I have to restate that my impressions are one of a clinician and I'm not an expert in insurance medicine or how you assess the risk. From a life expectancy standpoint, as a clinician, I see no substantial difference between applicants one, two and three and the general population. That's because they all should have no increased mortality from their ulcerative colitis.

Although they are all at some risk of colon cancer, we personally believe that the risk is extremely small and reduced by colonoscopy, because if a patient has pre-cancer changes, we remove their colon and remove them from risk. What I can't calculate as a clinician, as you do insurance individuals, is whether there's added risk from surgery, if you calculate that into your potential mortality.

I have to tell you I take care of one of the largest groups of patients with inflammatory bowel disease. We have about 4,000 patients that we're following in my practice at the University of Chicago and that includes about 2,000 patients with ulcerative colitis and in the series of patients that I follow, I've not seen a death of either ulcerative colitis or Crohn's disease in my 17 years of practice.

I have seen a few patients referred in from other physicians who had colon cancers who ended up dying, and we have seen a few patients referred in with sclerosing cholangitis who have had liver transplantation and when you add the risk of liver transplant now, which is about 80 percent survival from a liver transplant, we think that the prognosis is good for all these patients.

So I don't see a substantial documented increased risk for applicant number one, two or three, or any real way of differentiating between those three. Clearly patient number four is probably going to have sclerosing cholangitis; however, being that he is asymptomatic and having no elevation in the bilirubin, his immediate prognosis for the next ten years is essentially that of the general population. Patients with sclerosing cholangitis really only have an increased risk when there's evidence of jaundice or developing symptoms. Until that's the case, he probably is at no increased risk.

Whether or not he has the progressing form of sclerosing cholangitis or if he just has mild bile duct disease, should probably be evaluated with the ERCP. If I put myself in your shoes, I think the guy has sclerosing cholangitis. If the ERCP is positive, then I think he's probably at increased risk. If the ERCP is negative, meaning that he has small bile duct disease, I think he is probably not at any significant increased risk. So I take a much more benign stand than you do, but on the other hand, it's your money, not mine.

DR. PERMAN: Questions are invited.

AUDIENCE MEMBER: There are two questions that trouble me. One is that I've seen over the years about a half a dozen cases that start with a diffuse colitis and then result in proctitis or very limited left sided colitis. My question is where do you draw the line in terms of this is a localized or is it pancolitis. The second is, we've had some cases where there's been one attack, and then inactivity, no more symptoms, the patients refuse to go in for follow up. That's a problem for underwriting.

DR. PERMAN: Just for the record I will repeat. The first question is diffuse pancolitis going over into a more localized nice colitis and the other one is the one thing that you think is an ulcerative colitis episode and then they're quiet and not followed up.

DR. HANAUER: Those are excellent questions. Once the patient has had inflammation in any part of their colon from ulcerative colitis, we believe the whole colon is at risk. So that would be considered pancolitis. Now, there are problems in interpreting previous screening programs and the data on left sided versus pancolitis, as you heard from Dr. Rahn because in the early series the extent of colitis was determined by barium enema. Barium enema underestimates the mucosal extent, compared to

colonoscopy and colonoscopy underestimates the extent compared to biopsy.

So in that first question about a patient who had a pancolitis and has now more limited, the patient really always had extensive colitis although the activity is more active in the left colon.

Now the second question is also very interesting because the series of ulcerative colitis all have patients who had one initial attack and then no subsequent colitis. The question is did that patient have an attack of ulcerative colitis or was it a culture negative bacterial colitis? For instance, ten years ago we wouldn't have looked for cabalac jejuni as a cause of colitis. What we now recognize is that patients with acute self-limited colitis, meaning bacterial colitis, when they're colons heal their colons heal normally on biopsy, the histology is normal.

However, in almost all cases of ulcerative colitis, once the colon is healed, there is evidence of histologic architectural distortion. Even though there's no inflammation, the glands may be branched or distorted and most good pathologists can differentiate them. Now, the biggest problem that we see as gastroenterologists is the patients go to the doctor with a symptom of maybe they had bleeding or cramps and the doctors do a sigmoidoscopy or colonoscopy and take a biopsy and the pathologists interpret that as chronic inflammation.

Chronic inflammation in the colon is normal. Everyone in this room has chronic inflammation of the colon on biopsy, none of us hopefully have ulcerative colitis. So the term chronic inflammation is meaningless. What we're looking for, for evidence of inflammatory bowel disease, chronic inflammatory bowel disease is evidence of architectural distortion, far more relevant than whether or not there's a chronic inflammation in the bowel.

AUDIENCE MEMBER: The thought struck me, as the medical directors were talking about their ratings, that when you look in the impairment study I'm not sure where the cases of carcinoma in ulcerative colitis are coming from. I think you're comparing apples and oranges in the general population. Dr. Rahn related somewhat how to relate incidence of carcinoma in the non-ulcerative colitis population and then the colitis population.

These people are undergoing colonoscopies every year, they're getting their biopsies. The controls, or the age related non-colitis population aren't. Here you have a favorable population with not too severe disease or symptoms. If you give good credits to these people you could practically bring them down to standard I would think if they're under good surveillance. If they have any dysplasia of the slightest sort you can do a colectomy. What's with the table 468? I can't quite understand it, with the population that you're presenting in the case study.

DR. PERMAN: The question then: are we rating too high in terms of how the patients are followed? Who would like to take it up?

DR. RAHN: There are a lot of things. First of all, people don't always continue to undergo surveillance. The surveillance data is not as foolproof as we'd like to think. I think that you can be, optimistically at best, you can think that this person is being fairly compliant. You can't guarantee that. There's a high drop out rate in surveillance, especially in people who are asymptomatic. The other thing that you have to do is convince the person that he has to undergo a colectomy the minute you find some low grade dysplasia. That's not always the easiest thing to do either.

So I do think that there is some increased risk. In a 40-year-old who, if you take a 40-year-old compared to an aged matched 40-year-old other insurance individual, I still think that they're at a pretty significant risk, not tremendous risk, but a significant risk for having colon cancer develop sometime in their life span and perhaps limit their mortality. I think the other thing about colon cancer, something that we didn't say, is that it's a much more difficult disease to pick up on. It's a flat lesion. It's not so obvious as it is in a polyp situation.

The reason we use dysplasia is because colon cancer is flat and difficult to see with the naked eye, and as been alluded to, dysplasia is patchy and it's not foolproof, by any means, and there's varying thoughts as to what the statistics are as to if you find dysplasia, or you don't find dysplasia, more importantly does that person, will that person show up the next year with an invasive carcinoma. So I think based on that information, that's why I rated that person more highly. Maybe shave a table off for good behavior, but....

DR. HANAUER: My presumption is that you take a worst case scenario, you assume that the patients aren't going to be compliant and you have no way of assuring yourself of that. And you have no way of predicting the outcome of liver transplant.

DR. RAHN: I think from the life insurance perspective, when we look at someone who is 40, in order for them to be a standard risk, they have to live until late in their 70s or early 80s, therefore that risk is, if somebody lives ten years with PSC, that's not good enough for a 40-year-old from a life insurance perspective. That makes their mortality, they would die, say, at age 50 or 60, that is unacceptable. They can pay enough premium to cover immortality because standard mortality is closer to 80.

AUDIENCE MEMBER: First is just a comment. I think when we're talking about ratings of 200 percent or so, you're not talking about too many years of change of life expectancy. I don't have the tables in front of me but I'd say somewhere between three and five years. My question regards the colonoscopy and it's in two parts.

I detected a little bit of disagreement in the frequency of colonoscopy and biopsy and I wonder what is the gold standard. The other is, if a person just had a left sided disease and it stays that way for a few years, chances are it's going to stay left

sided disease. Are we going to be at some point satisfied with a limited colonoscopy to the left side?

DR. HANAUER: The standard of colonoscopy is evolving right now. It's evolving two ways. One is we don't know the most cost effective way to screen. We published one series based on the mammography experience, where since the risk increases as the duration increases, it makes no sense to have a standard yearly colonoscopy from 10 years on. So currently we recommend between 10 and 20 years of disease to have a colonoscopy every three years, between 20 and 30, every one to two years, and then after 30 years of disease, we begin yearly colonoscopy because the yield before that is very small, the rate increases.

Now, the problem has been that even to this day, as Dr. Rahn has mentioned, low grade dysplasia has not been generally accepted as the determining point to perform a colectomy and those of us who are more and more experienced with this and have continued to review the data are more and more reassured that if you want to prevent colon cancer, you have to act on any evidence of dysplasia and do a colectomy if there's any dysplasia.

It's just like if you had a woman with a mammograph who had evidence of dysplasia on the mammogram not to act on that would be the wrong thing. Of course, that just may be a lumpectomy or whatever, but the point is the whole colon is at risk, dysplasia is focal and the only way to save lives, as Dr. Rahn and as we have quoted Dr. Sacher and our other colleagues, is to remove colons with any evidence of dysplasia.

There are, by the way, Europeans who have suggested, and the Danish population and in even the Swedes in the past have recommended a colectomy in anyone with ulcerative colitis after ten years of disease. That is no longer the case, but some people were as conservative as to make that recommendation.

AUDIENCE MEMBER: The second part of the question, maybe you answered it, even with left sided colitis, the whole colon is at risk?

DR. HANAUER: For cancer?

AUDIENCE MEMBER: Yes.

DR. HANAUER: Probably more the left side, but that data is muddled by the fact that the general population has a greater risk of left sided colon cancers. So we really can't separate that very much. The risk is so much smaller than the general population and the number of cancers of the left side of the colon are relatively small and you have to separate it from right colon and you have to know the biopsy extent of the disease besides just the colonoscopic or

X-ray. So that data is virtually, it's not been sorted out.

AUDIENCE MEMBER: How many biopsies do you have to have before you say there is no dysplasia?

DR. HANAUER: Again, it's controversial. In our series we biopsy every ten centimeters, which is about ten biopsies of the colon. As I stated, the negative predicted value in our series of looking at colectomy as the gold standard of whether or not there truly was dysplasia was the negative predictive value, meaning if there was no dysplasia, we had more than a 95 percent likelihood that there would be no dysplasia at colectomy. So we're not missing very much.

AUDIENCE MEMBER: What about one biopsy?

DR. HANAUER: No, it's not satisfactory. Nor is it satisfactory only to biopsy the rectum. The history of that was that in Leonard Jones' group in London they had recognized that there were biopsied patients who had rectal biopsies had dysplasia. So people began to just biopsy the rectum and that clearly is not sufficient.

AUDIENCE MEMBER: These are cases with high amounts and rather well documented. What do we do with a $30,000 case where we know very little or nothing about compliance, where we have no other major parameters to forecast properly? My question is, what we have in each and every case, for example, the body weight and height. Is there any more modern tumor marker in the pipeline because the one you have mentioned I think we can forget. These are my questions.

DR. PERMAN: The first is our every day life where we have to make decisions on incomplete material. It might be very difficult for Dr. Hanauer to express anything than sort of regret and sympathy as far as that point. But perhaps you have something to contribute and also the tumor marker I think is an important question.

DR. HANAUER: My answer to the individual cases where you don't have information is going to the standard mortality ratio and in recent series that seems to be the same as the general population, with ulcerative colitis as a whole. So I don't have as much sympathy for your rating these patients higher because the data seem to suggest that compared to age matched controls, there is no excess mortality, taking into account all the other diseases that are out there.

As far as additional tumor markers, I am not as pessimistic about dysplasia as you are but the rest of the world doesn't have the expertise that a few of our centers do. Yes, there are other markers in the pipeline. They're, of course, at the moment more expensive. Also we have to take into consideration a group of patients who are predisposed to colon cancer in general with the new genetic markers that are coming out that have not even been looked at yet in ulcerative colitis. The rason cagene has been looked it. It's no better than histologic screening, but of course we are actively seeking other markers.

AUDIENCE MEMBER: I'm referring to the last question. In our day to day work, if we have a patient with ulcerative colitis and slightly elevated liver tests, could you give us a threshold for

these liver tests and which tests would you say is most significant for saying that PSC is present because in our daily work we can't send some for an invasive procedure, so what would you say about that?

DR. HANAUER: I would say that you do not see pericholangitis, the benign form, in patients with transaminase levels more than twice normal, and certainly not with elevated bilirubin. So if I see less than twice normal transaminase and normal bilirubin, I'm not so worried about the alkaline phosphatase and the GGTP.

AUDIENCE MEMBER: A comment to maybe explain some of the discrepancy between our GI consultants' assessment that mortality is basically normal and the insurance industry's experience is it is not. It is very rare indeed for any medical literature to follow any disease process for four years. When we read journals, it is very rare for them to follow it for ten years.

The Framingham study is the only long term study that is even approaching four years. What would appear to be normal mortality extrapolated from five and ten years studies, our industry suggests that may not be so. That's a comment, not a question.

DR. PERMAN: I must say personally I was impressed with Dr. Hanauer's statement about his 17 years experience and 2,000 patients with no deaths.

DR. HANAUER: No deaths from ulcerative colitis. There obviously are deaths from other illnesses, routine non-ulcerative colitis deaths.

AUDIENCE MEMBER: Which time do we cover a five-year, a ten-year, a 20-year, a 30-year insurance cover? That's the first question. And this is very important because I come back to plead upon you of a relatively positive liver transplant, a 20 percent life expectancy. This is very important for our daily business and I think I should ask this question.

DR. HANAUER: I think the data only goes, for liver transplants, this only goes out for five to ten years. So I can't extrapolate. If it were my money I wouldn't invest longer than that.

DR. PERMAN: Do we have any more questions?

AUDIENCE MEMBER: Is there a difference between colitis with and without sulfasalazine?

DR. HANAUER: Not that we can say. You mean with the newer agents, the macalamine agents? No, there's no data on that. There's no reason to expect that it would be different.

MR. PERMAN: This question was not planted, may I add, but sulfasalazine was invented in Sweden, sold by a Swedish company.

AUDIENCE MEMBER: I have two questions. I have a reference here that relates Canadian experience and they show differing mortality for males and females and they're looking at current, 1987 and 1989 treatment. That makes quite a difference to us because when we look at mortality ratios, of course, ladies have lower expected number of deaths so if they indeed do have a higher death rate due to ulcerative colitis, then that makes them far off standard.

So my first question is, is there a difference in male and female mortality and secondly, how far are we from being able to do stool specimen checks for pre-malignant cells using genetic tests?

DR. HANAUER: I can't comment very much on the male/female because as a clinician, I don't pay attention to that data very much and I honestly can't contribute to that.

We are not very far from being able to look at sidametric changes and cancer markers in the stool. That's probably just a few years away. But then the long term applicability will require additional studies, especially in these diseases.

AUDIENCE MEMBER: There are a number of markets that would suggest that because of a confidential nature, genetic information, that it's unique and insurance companies perhaps shouldn't have access to that information. Would you comment regarding whether or not you think that this stool test would be a genetic test of disease in progress as well and therefore it should be shared with insurance companies.

DR. HANAUER: I understand but I'm trying to assimilate that question. I think that this is a tremendous area for future insurance ethisis. Since we now know that there is a breast cancer gene, are you going to insist on genetic tests on every woman to know if she is one in the eight who carries that gene? That's the same sort of question.

AUDIENCE MEMBER: I'm really asking about cancer in progress, monitoring the genetic status of a disease in progress. Not in 20 years are you going to get cancer or are you going to get ulcerative colitis. We're now checking specimens looking for the genetic equivalent of dysplasia.

DR. HANAUER: At the moment those tests are not available or relevant, so I can take an easy out on that point.

DR. PERMAN: Any more questions from the audience? Okay. Folks, we have had a very lively discussion and we have actually used a little bit more than the time we were allotted. I must say, to me the overriding message is aren't we a little tough on the garden variety of ulcerative colitis patient? We must first of all thank Dr. Hanauer for coming here and giving of his expertise. We were obviously very lucky to have this subject in Chicago. I would also like to thank all the medical directors who have given much of their time to sort out the thinking around their risk evaluations. With that, I'd like to close this forum.

(Applause.)

(The meeting was adjourned.)