SCREENING AND EPIDEMIOLOGY

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DR. SCHWARTZ: Thank you very much. From our point of view, screening is the pot of gold at the end of the rainbow. If we can find tests that will help in the early detection of cancer, we can fulfill our intuitive feelings that early detection leads to early treatment, which in turn leads to cure. Certainly we know that early treatment of breast cancer or colon cancer results in very much improved survival rates.

The problem is emphasized by the latest cancer incidence data. The '92 estimates of cancers in the United States suggest that there will be a total of 1,130,000 cases this year, with 520,000 deaths. I hope to emphasize during my presentation which cancers are amenable to screening and which are not. It is highly unlikely, for example, that we would try to screen for pancreatic cancer when each year there are 28,000 cases in the United States and 25,000 deaths. Lung cancer is another cancer where screening might not be useful. A screening test must detect the cancer early, and the therapy that is initiated as a result of detection by screening must be more effective than therapy undertaken at diagnosis, when there is clinical symptomatology.

A definition of screening was established by the United States Commission on Chronic Diseases. It’s the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures that can be applied rapidly. This is different from case-finding, when a patient presents at a physician’s office and during the course of evaluation tests are done and a disease is detected which is not related to the initial complaint of the individual. As Dr. Herberman pointed out, screening can be done in general populations or in individuals at high risk.

To emphasize what we mean by high risk patients, we can look at colon cancer. In colon cancer, certainly, all asymptomatic individuals over age 50 are subject to screening. Those with a family history of colon cancer or polyps are subject to screening. And, individuals who have a past history of colon cancer, breast or endometrial cancer, or who have had radiation therapy are at much greater risk for the development of the cancer and therefore might be subject to screening. This definition of high risk groups can be made for every cancer.

Here are the 1992 American Cancer Society recommendations for screening. If we go through this list, you’ll see that there isn’t a single tumor marker, as defined by Dr. Herberman, that is included on the list. The list includes sigmoidoscopy ever three to five years for individuals greater than age 50; stool guaiac yearly in that same group; digital rectal exam yearly after age 40; PAP smears at age 20 and then three annually, and if they are normal thereafter at the discretion of the physician; a yearly pelvic examination every one to three years and, over age 40; obtaining at menopause endometrial tissue for histopathology; breast self examination, monthly; breast clinical examination every three years, and over 40, yearly; mammography every one to two years between 40 to 49, and yearly after 50; and a health check up, which means a visit to a physician every three years for individuals over 20, and every year for individuals over 40. The question is, how good are these tests? Dr. Herberman alluded to the fact that mammography may not be as good as some people are led to believe. If individuals have a breast cancer equal to or less than one centimeter, on clinical examination untrained women can only detect 55 percent, registered nurses 65 percent, and physicians 87 percent. Mammography is 70 percent reliable, and in individuals greater than 50, it’s 87 percent. But in younger individuals it’s less than 60 percent, which is surprising. Self examination, which is stated to be a very important breast cancer screen, is only 34 percent reliable for all individuals. And in older people who have more difficulty in doing breast cancer examination, it’s only 21 percent effective. Fecal occult blood only picks up 20 to 25 percent of colon cancers, digital rectal examination is less than 10 percent, and sigmoidoscopy detects 50 to 60 percent of colon cancers. The PAP smear is the best of them all, with greater than a 90 percent detection rate. Yet depending on the report, these are 20 to 40 percent false negatives. In prostate cancer, DRE is 69 to 73 percent effective, ultrasound 31 percent and serum acid phosphatase only 20 to 25 percent. So, you can see that screening today does not achieve what is needed. And if you examine PAP test screening, you see that doing a PAP smear on a yearly basis increases life expectancy only 67 days at a cost of $315.00. With lower testing frequency, you decrease the increased life expectancy to 53 days and the cost to $54. However, it is clear that PAP smears brings about much greater improvement in survival and quality of life.
Recently in the Healthy People 2000 program information was presented concerning the health status in our country in 1987, and the proposed achievements in screening tests by the year 2000. Interestingly, in 1987 only 35 percent of the eligible population ever had a mammography. By the year 2000 we hope 80 percent will. It is proposed to increase PAP smears from 88 percent to 95 percent with one done in the preceding three years in 87 percent of the population. Fecal occult blood testing was only done in 27 percent of the population in 1987. It is proposed to increase this to 50 percent by the year 2000. An important point about mammography and PAP smears is the quality of the procedure. It is essential that the American College of Radiology certify those instruments and those individuals who perform mammography, and that all cytology labs be certified. There is no data (believe it or not) on just how many laboratories which perform PAP smears are truly certified.

We are going to talk about circulating markers primarily, and how we can use them. We’ve already heard about sensitivity and specificity. If you’re going to do screening, you really ought to do it for a disease that is important and is common, and that results in substantial mortality and morbidity. Certainly breast cancer, lung, prostate, and ovary would fit that criteria. We must know enough about the natural history of the disease to know at what stage of progression death can no longer be prevented. Pancreatic disease would not be a good candidate, as I mentioned, because death probably cannot be prevented. Lung cancer would be similar. There’s no point in screening for a disease for which there is no effective treatment. Last, but not least, and an important problem for those of us who are involved in laboratory medicine, is convincing the physician and the patient that these tests are of value, and they will accept them.

What are the criteria for an acceptable screening? Certainly, a test that can pick up 75 percent of cancers at a time when no more than ten percent of them have spread, and a test that only gives five percent false positives, would be something for us to strive for. None of the tests that I will discuss today, or perhaps any of the other speakers will discuss, have achieved that degree of sensitivity or specificity. Dr. Herberman mentioned the use of alpha fetoprotein for screening in China where hepatocarcinoma is endemic, presumably because of the prevalence of hepatitis B. In early data after screening less than a half a million people, 147 individuals exhibited an elevated alpha fetoprotein. They finally detected 53 liver cancers in these patients of whom 33 were asymptomatic individuals. In 3,619,000 patients who have been screened, there were 782 positives of which 301 cases were asymptomatic. The expected prevalence would have been 1403. They detected approximately 50 percent of the expected cancer patients. The question might be asked, “Why, in a country with more than 1 billion people, would you expend so much effort to detect 301 individuals with hepatocarcinoma?” I think screening in the Far East is cultural as well as scientific. There is a great family relationship, and a need, from their own point of view, to do this.

An important point in screening is the analytic sensitivity of the test. When an assay measuring the diameter of immunochemical diffusion into an agar gel was used, hepatoma was detected in 39 of 56 patients. There were no elevations in hepatitis, cirrhosis, or other kinds of disease, perfect specificity. But, when new technology, a radioimmuno assay which increased the analytic sensitivity of this test 1000-fold, was used the pick up increased to 49 of the 56 hepatoma patients. But there was so much "noise," so many false positive elevations in other situations, that it made it useless as a screening test. So, a caveat in screening is to adjust the cutoff to do what you want it to do.

Another use of screening is for neuroblastoma (which is a very rare cancer) in Japan. The data demonstrate two things: Screening leads to more and more expensive tests and the cultural aspects in Japan concerning screening. In Japan, they now screen for neuroblastoma in all newborns. There is a very simple paper strip screening test which can lead to additional testing. In Nagoya they reported a screen on 21,000 patients. By doing increasingly sophisticated tests, and bringing the children back for further testing, they eventually ended up with five positive out of the 20,000 screened. I calculated that cost, when the yen was 240 yen per dollar, at about $10,000 per positive test. The Japanese feel this is very useful because these children are "cured," are not institutionalized and return to their families. A similar study, but with clinical follow-up has been carried out in Kyoto, where they’re now up to about half a million children. In this study, there were 25 positive patients followed for 20 months or more. Of these, 92 percent are completely free of disease. The interesting aspect of this rather extensive, rather expensive program is that in all of Japan there are only 220 cases of neuroblastoma each year. Statisticians concluded they would only detect 135 to 146 patients with this screening. I doubt we would entertain such a screening program, although there have been attempts in some states to initiate it. In Minnesota and even in New York there have been attempts to do that.
We talked about fecal occult blood screening, and this is generally considered to be the simplest of tests. We as patients are routinely asked to collect a specimen and submit it for analysis. Data from a national polyp study indicates that fecal occult blood is not a fool-proof test. The national polyp study has centers throughout the country which are involved in the evaluation of polyps. When this study was started the individuals who had been assigned to do the fecal occult blood testing were brought together for proficiency testing. When they first came, they were able to detect only 38 percent of the known positive slides. After they had training it went up to 90 and then 94 percent for moderately positive slides, and from only 78 percent up to 100 after training for very strongly positive slides. So, even this simple test requires performance by someone who is trained.

An interesting study sponsored by the Office of Science and Technology of the United States Congress appeared recently. (Ann Int Med 1991; 115:807.) They proposed a theoretical evaluation of fecal occult blood testing annually or a combination of fecal occult blood and sigmoidoscopy in all men at age 65. Their evaluation took into account all of the possibilities: the treatment of latent diseases, the risks of sigmoidoscopy, etc. The net cost of the fecal occult blood screening and sigmoidoscopy in this country would be 2.63 billion dollars, and if you did only fecal occult blood it would be one and a half billion. But what would you achieve? (Remember I said there are about 150 thousand cases each year.) You would detect 33,000 cases if you did both, and 22,000 if you did only the fecal occult blood. The cost per year of life gained would be $42,000 and $35,000, respectively. Looking at this cost, you might conclude that a Congressional office would deem it not valuable or worth doing. However, their conclusion was that screening for colorectal cancer is a reasonably cost-effective preventive intervention for the elderly. They claim that it is no more expensive than a mammography program, and less expensive than doing dialysis for end-stage renal disease. Of course, there's a footnote that the viewpoints in this paper do not necessarily reflect the position of the Congress of the United States.

Now just a bit about tissue. You probably can't see this slide. This is the elegant work of Vogelstein and Associates at Johns Hopkins. It shows the development of colon cancer, from normal epithelium to carcinoma to metastatic disease. These are genetic changes which occur, perhaps over a 20-year period. If we had some simple way of measuring these changes, it's not beyond belief that we could isolate a group of individuals who are at high risk for colon cancer 20 years before that catastrophe occurs. We must have the technology to detect the chromosome gene alterations. However, one cytogenetic technologist, in our institution, can evaluate about 50 patients a year. So, we're far from being able to do it on a mass screening basis, but certainly it's on the projected table of things to be done. All of these things occur over a ten-year period, and they are all measurable.

Well, let's talk about ovarian cancer, and the use of CA125. Dr. Herberman referred to it. I was in a plane coming back from Seattle last week and I picked up a copy of a magazine; I think it was Town and Country. There was an ad with Gene Wilder's picture, talking about his wife, Gilda Radner, who died of ovarian cancer. The theme is, be sure to ask your physician to do CA125. The ad was sponsored by one of our large cancer research centers. CA125 is elevated in a large number of patients with cancer of the ovary. If you use 35 units per milliliter as the cutoff, it's also elevated in a percentage of benign patients and in other cancers. (Cancer Research 1984; 44:1048.) As you go up with the cutoff, as Dr. Herberman showed, you reduce the number of false positive normals. Using elevations to 65 units, you only have two percent benigns, two-tenths percent of normals and you've only reduced the ovarian cancer pick up from 82 percent to 73 percent. But, you still have a large percentage of other cancers that are detected. At 220 units per milliliter you have no normals, but, again, a certain percentage of other cancers. So the question is where would you go if you want to use it to screen? Or can you screen? Or should you screen? If you even try it, the cut-off should be between 65 to 220 units. Unfortunately, from the point of view of screening, CA125 is elevated in many other situations. It's elevated in about 14 percent of individuals who are pregnant, with values reported in the literature up to at least 500 units. During menstruation it can be elevated, in benign endometriosis, in adenomyosis, these are very high levels and in some instances, such as benign ovarian cysts, up to 2000 units. CA125 exists on pleura, so any disease that brings about inflammatory change of the pleura can lead to an elevation. In benign lung disease you see elevations up to 270 units in 43 percent of persons with asthma and pneumonia and a variety of other things. In peritonitis it can be up to 500 units. Up to 60 percent of women with pelvic inflammation had elevations up to 1300 units, and in ascites it can be up to 500 units. So, here we have a test that has been proposed as a tumor marker, but it must be viewed with the understanding that there is a whole list of conditions where CA125 will be elevated.

This is later data on screening with CA125. (Zurawski et al. Gyncol Oncol 1990; 36:299-305.) This was a study of 1082 women over 40 years. When CA125 was greater...
than 35 units per milliliter, they found 3.3 percent were elevated. If you use over 65 units per milliliter, they had 11 positives and 1.7 percent would be considered false positives, because these women did not have symptoms. Remember, we don't have a true definition of a false positive in cancer, because "false positive" is a real-time definition. It doesn't take into account the lead time, and if you have a "false positive" today and a cancer develops six months from now, was that truly a false positive? In this study they found great individual variation, and they tried to find some way of evaluating CA125 as a screen. They decided to do second assays, and those individuals who had a doubling of the level were considered to be truly positive. Of those 1082 women, there were two who demonstrated doubling of their values, and one had the clinical diagnosis of stage 3 ovarian cancer established 21 months later. So, one in a thousand had an eventual cancer. The question is whether this is an appropriate screen? It is my view that it probably is not, but there are others who might disagree with that.

CA15-3 was mentioned by Dr. Herberman. I want to state that we do not have a tumor marker screening test for breast cancer. CA15-3 has been proposed for that. In a study of over a 1000 women, with a cutoff of 50 units, you would find that there are 13 percent of the breast cancer patients who had elevations and only two percent of the normals. Thirteen percent might be something that's acceptable, but probably not.

Now, let's go to prostate cancer, which I said has led to a great deal of excitement recently. This was a memorable study a number of years ago that placed laboratory tests in proper perspective. (N Engl J Med 1980; 303:499-503.) The study showed that an educated finger (digital rectal examination) is the most important way to diagnose prostate cancer. 300 patients had a digital rectal exam with a predictive value for positives of 67 percent, and for negatives of 91 percent, with an efficiency of 85 percent. Whereas acid phosphatase, urine cytology, and aspiration cytology were not as efficient. Everyone then accepted that a digital rectal exam was the best method of detecting prostate cancer.

However, PSA has come on the scene, and the question is, "Can it be used in screening?" This is our data, and it indicates something that is quite different from anything we were able to do before. With PSA we are able to detect a large percentage of men with early prostate cancer, stage A, that is prostate cancer which has not yet reached the membrane of the prostate and cannot be detected by palpation but only by histopathologic definition. It is usually only a coincidental finding during a prostatectomy for benign prostatic hypertrophy (BPH).

Using four units as the cutoff, you can detect Stage A and B prostate cancer in a large percentage of patients. But, there's a fly in the ointment! This is data from a cancer detection clinic, where 28 percent of 192 men with benign prostatic hypertrophy also had elevations. (Oncology 1991; 5:107-126.) Although we can detect a large proportion of men with Stage A and B, we also have a large number of men with BPH who have elevations. As you raise the cutoff to 6, to 8, and finally to 10, you bring down the positivity in the detection clinic to 8 percent. Some of these men (between 4 and 10) may very well have had cancer, since BPH was not confirmed by biopsy. When you increase the cut-off level, you reduce the detection rate of Stage A to 25 percent and for Stage B to 37 percent. You end up with about 30 percent detection of early prostate cancer and very few BPH patients have elevations.

In another study, a large group of patients with early prostate cancer was detected and only five percent of the men had BPH. So, by going to a cutoff of 10 nanograms per ml it is conceivable that you can pick up a large group of patients with prostate cancer, in this study about 20 percent with only 3 percent elevating BPH. The specificity was 96 percent, and the sensitivity was 23 percent.

If we consider a theoretical screen for detecting prostate cancer in 100,000 men, with prevalence at either 10 percent or 5 percent, sensitivity at either 75 percent or 25 percent, and specificity at 95 percent, we will obtain the following data. In these 100,000 men there would be 10,000 cases of prostate cancer, a 10 percent prevalence. The true negatives would be 85 percent. (You'll have to trust my math, but you can check it out at your leisure.) So, 85,000 would be true negatives. But, you'd have 4500 false positives along with true positives of 7500. You would actually have 12,000 positive values. You would have picked up 75 percent of the cancer patients. Now, if you go down to a sensitivity of 25 percent (which is really about where PSA is), you'd still have 85,500 true negatives, and you'd still have 4500 false positives. But, your true positives now would be 2500 and the false negatives would be 7500. So now you'd have 2500 out of 7000 positives that you'd have to deal with. The question is, how do you deal with them? How do you deal with the false positives? What is the psychological problem of telling an individual that they have a positive test and must undergo a whole bunch of difficult and expensive diagnostic tests, etc. If you assume a prevalence of five percent, the data is about like this: 4750 false positives, true positives of 1250, so you end up with 6,000 positive values of which only 1250 would be actually have cancer. This is the problem. How do you divide the false positives from the true
positives in this population? The false negatives are of no great concern because they would have been negative anyway. To the insurance industry, of course, the false negatives may be a very serious problem, because those diseased people would not be detected.

An interesting cost evaluation has recently been proposed on screening with PSA. (Urol Clin North Amer 1990; 17:719-737.) It was proposed to screen all men between ages 50 to 70, excluding those with cardiac, pulmonary or malignant disease. In the United States, there would be 17,496,288 such men. To screen them all on a theoretical basis, digital rectal examination (DRE), transrectal ultrasound (TRUS), and a PSA above 10 were compared. True positives would be 1.2 percent with DRE, 7.3 percent with TRUS, and 4.4 percent with PSA.

However, the false positives would be the lowest with the PSA. With TRUS you'd have up to 18 and a half percent false positives. The false negatives would be similar throughout, but the true negatives would be much greater with PSA than TRUS. The total cost for this program, if you did transrectal ultrasound, would be 23 billion; digital rectal exam would be 17 and a half billion; and PSA would be 11 billion dollars. The authors went on that in the United States at this time there are only about 24,000 men being treated for prostate cancer, at a cost of only 255 million dollars. They estimated that from 0.05 percent of the total expenditure for health care in the United States related to prostate cancer, the screening program would increase costs to over five percent of total health care cost.

The excitement about PSA increased last year, when an article entitled "Measurement of prostate specific antigen (PSA) as a screening test for prostate cancer" appeared in the New England Journal of Medicine. (Catalona WJ, et al. N Engl J Med 1991; 324:1156-1161.) Of course, this was picked up by the New York Times, the Wall Street Journal, and other "scientific publications." The conclusions reported in the media were not quite the conclusions reached by Catalona and his group. The study was done in St. Louis, where advertisements were put in the newspaper and men without known prostate disease were asked to volunteer for study. About 1600 men appeared who were determined to be in that category. Any man who had two PSA values of less than 4 nanograms per ml over a 6 month period was told to go home. No further clinical studies were done on them. This was, in my opinion, a flaw in the study, that there were no digital rectal exams, no ultrasounds on these men. The study ended up with 107 men who had elevated PSA at levels from four to ten. They asked these men to volunteer for a rectal exam and ultrasonography. If one or both was abnormal or suspicious, needle biopsy with ultrasound guidance was done. When the PSA was over 10, which was true in 30 men, they did ultrasonography and a biopsy. Biopsy was the end point for the 137 people with levels over 4. The results were compared to a control group of men who were coming to a urology clinic with symptoms of prostate disease. It was found that the data were almost identical, whether the men had symptoms or did not, and this was the data upon which the conclusion was reached that screening was appropriate. In the 107 men with PSAs between 4.1 and 9.9 there were 22 percent biopsy positive, while the men who went to the clinic with these PSA values had 26 percent biopsy positive results. In those with levels greater than 10 from the screening study, 67 percent were biopsy positive, and those greater than 10 from the clinic had 64 percent positivity. The data in the two groups were identical. Now, the treatment of prostate cancer and the diagnostic tests for prostate cancer are not innocuous. If you did the theoretical screening program in the 17 million men I described earlier, it was estimated you would end up with 266,000 impotent males, 61,000 incontinent males, 10,000 men requiring colostomy, and 20,000 men with treatment-related deaths. So, when you undertake a screening program you ought to know the consequences of the treatment.

Now one last study about PSA, indicating that PSA is probably as good as digital rectal exam. (Am Clin Lab Sci 1990; 21:371-380.) Each year we have national prostate awareness week, and we are now beginning to ask men to be screened with PSA. This is a study done in two upstate New York counties, Madison County and Oneida County, during Prostate Awareness Week. Over 1000 individuals were examined. DRE alone was not very good, and PSA alone was not very good either; about 24 percent of positives actually had cancer. But if you put DRE and PSA together, and they were both positive, as was true of 16 men, then 69 percent were found to have cancer. A combination of digital rectal examination and prostate specific antigen increased the detection rate.

A very interesting study was done in Britain in one of the National Health Service Units. (Chadwick, et al. Lancet 1991; 338:613-615) indicating that PSA may have a role when non-urologists are doing the digital rectal examination. This was done in Bristol where 7 GPs represent a population of 13,000 individuals. They screened all the men in their unit who were between 55 and 69 years of age. They didn't get them all, but they asked them all to come for screen and they ended up with 472 who responded. 407 of these had DRE and 437 PSA. They found that 62 of them had PSA greater than
4, only 12 had abnormal DRE, and one had both abnormal PSA and DRE. The final conclusion is that they detected 7 cases of prostate cancer based primarily on PSA, but they had a very low detection rate with digital rectal examination. They concluded the GPs are not very skilled in performing digital rectal examination. Their cost was $1654 per case of prostate cancer, and they have recommended to the National Health Service that screening with PSA be done.

I just want to show you this. I don’t know if you can read it. This reflects the current status of PSA screening. I was in California two weeks ago and an individual handed me this. They had circled digital, because they couldn’t understand what was meant by digital. They thought it had to do with counting. I explained to them that it was a finger.

This is from UCLA: "Free prostate cancer screening in men over 50 years with no history of prostate cancer." "Exam performed by UCLA physician." "Takes only 15 minutes." "PSA blood results sent to patient in two weeks." And, "Discounted parking in the Medical Center parking lot." (laughter) So you see, we’ve really gotten into the act of doing prostate screening.

Now you have to know a few things when you’re going to do PSA screening. (Oncology 1991; 5:107-126.) The half-life is two to three days. And, elevations may occur after manipulation, ultrasound, and/or biopsy. There is no circadian pattern, but we do observe six to seven percent variation in several specimens collected during the same day. Ambulatory values are higher than sedentary values. In fact, I can "cure" prostate cancer by allowing the patient to spend 24 hours in bed, since the value will fall approximately 50 percent. And, different assays yield different results. This is really a very important consideration which we will get to in more detail this afternoon when we discuss the real world. The fact is that different assays can give numbers differing by as much as two-fold.

Now, I was asked to discuss for a moment whether there is a "universal" tumor marker. All of these tests I’m going to show you have one problem that must be solved - very few patients in the studies. We need to have good clinical trials of new tumor markers. Perhaps these studies can be funded through the insurance industry, which obviously has vested interest in learning about them. This is a tumor-associated antigen in melanoma. (Inter J Cancer 1990; 45:1065-1070.) 63 percent of patients were elevated, but in mass evaluation of urine, elevations were detected in 4 percent. Not a very high degree pick up.

(Cordon SG, et al. Cancer Research 1991; 50:6229-6234.) Cancer procoagulant (CP) is a protein, a peptide. In fact, it’s a cysteine protease. It is involved in the coagulation process and was being studied because of interest in the abnormal coagulation in patients with cancer. Almost all the patients had elevations; obviously there is need for detailed studies. Antimalignin antibody (AMA) has been with us for a number of years, and we need controlled studies of this maker. The most recent literature, and I thank Dr. Bogoch for sending it to me when he heard that I was to discuss markers and screening at this meeting, is a study of 677 symptom-free, high-risk male individuals. It was published as a letter to Lancet. You see there are 683 tests on 677 patients. According to this data, 574 were healthy, 26 had benign conditions, and 18 were symptomless cancer patients. There were only 59 cancer patients. Patients with terminal cancer were excluded, as predicted by their low AMA concentrations, and all of those died within a year. Another study of the same kind was in the Proceedings of the American Association of Cancer Research in ‘90, but again, had only 19 cancer patients. If we’re going to use any of these tests we need to have large studies with large numbers of people. A study in the New England Journal that raised a lot of interest several years ago was of nuclear magnetic resonance of serum. In the initial data there was an obvious, absolute cutoff. Unfortunately, these studies have not been duplicated. This was proton nuclear magnetic resonance, and C13 magnetic resonance is now under evaluation. These assays require specimens to be collected and shipped in a very, very careful fashion. The antimalignin antibody assay also requires specimens collected and shipped in a very special fashion.

In conclusion, I’d like to say these special tests should not be overlooked. Winston Churchill said, "Men occasionally stumble over the truth but most of them pick themselves up and hurry off as if nothing had happened." We should consider the fact that a positive tumor marker can be very meaningful, but a negative tumor marker cannot and should not give anyone a false sense of security that cancer is not present. Thank you very much. (applause)