X-RAY BACKSCATTER AND THE POSSIBILITY OF CANCER

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Abstract

This report looks at x-rays and especially in the context of low power backscatter systems. It presents an overview of the key technical issues regarding the generation, detection and processing of backscatter and the image processing related thereto. Then we look at the current systems in operations. Finally we look at the issues related to melanoma and the pathways associated with that disease. Then we demonstrate that using backscatter system we also can potential initiate changes in the pathways which may lead to metastatic melanoma. This paper is a review of some basic principles of X-Rays for the purpose of then examining their use in backscatter systems and in further examining the potential for cancer by the repeated use of such systems. The major concern is that albeit low energy X-Rays are used, that they are used frequently and are absorbed several layers below the skin and that for individuals with a predisposition for skin cancer, melanoma, that this extended use of backscatter could result in substantially increased risk.

1 INTRODUCTION

Backscatter radiation, albeit of low level, is still ionizing radiation. The deployment by TSA of hundreds of systems at US airports and the repeated exposure of people raises the risk of certain types of cancer. This paper looks at the risk for a specific type; melanoma. Why look at this? Because, with backscatter, almost all the radiation is delivered over only a 1 cm thickness, the epidermis and dermis, and also because there is well established proof that ultraviolet radiation causes melanomas and the energy in backscatter is orders of magnitude greater.

1.1 THE CONTROVERSY

The NY Times wrote an article a while back on the potential risks of x-ray backscatter at airports[1]. Since then the TSA has deployed hundreds of x-ray backscatter systems which employ ionizing radiation on millions of people. Let us take another look at this issue.

X rays are very powerful electromagnetic waves which are generated by colliding electrons[2]. The x-ray is of very short wavelength, very high frequency and has tremendous energy.

We use strong x-rays now for over 100 years to look within the body. Namely we put the x-ray gun on one side and the file, well very few use film any more, on the other and look at what happens in between. We can see broken bones, tumors, and the like. A great advance except for one tiny problem, x-rays break DNA bonds and other such stuff and that results in cancer.

Now the powerful x-rays that go through the body are transmitted, namely they come from behind a molecule and then are absorbed or allowed to pass through. Thus the lightness and darkness. The deeper we want to go the stronger we make the scan, namely more x-ray photons. Yes, x-rays are particles, photons, but at the frequency of the x-ray. Thus the same energy per photon is used but just more photons. CAT scans use lots of photons. CAT scans are also transmission in nature, going from one side to another.

Now there is also a scattered x-ray approach using what is called Compton scattering. You see the x-ray has a wavelength similar to that of an electron, one of the electrons in the outer rings of the atom, and when it hits one of them it bounces the electron out of orbit, the x-ray loses energy and it gets scattered at a lower frequency backward and the atom is now missing an electron. Then what happens. Two things:

[1] http://www.nytimes.com/2010/01/09/health/09scanner.html

[2] http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM231897.pdf The FDA allows specific members of its staff to opine regarding the safety of backscatter despite the fact that no large scale tests have been performed. This is unheard of with all other parts of the FDA. They seem to be relying solely upon industry standards groups who compare gamma rays, x rays and other forms of radiation. Other industry reports provide mixed data comparing all forms of radiation. http://www.iscors.org/doc/GSSHUIR%20July%202008.pdf . Here we focus solely on x rays and solely on backscatter and skin related lesions.

1. The scattered electron comes back and can be measured as backscatter

2. The poor atom is now looking to fill the electron loss and something, somewhere, will fill it. That is where the real problem comes in. If this were a cytosine on your skin DNA, say the DNA of a melanocyte in the basal layer of the epidermis it may get methylated. Then we start the process of carcinogenesis. Then we start a melanoma. You do not need a great deal of energy, you are not going through the body, you just want backscatter, and what you are backscattering off of is the skin! And if a person has dysplastic nevus syndrome, their melanocyte DNA has already had many hits, or if the person has extensive sun damage, the same. It then takes just one more hit on a single cell DNA, and off we go to the morgue!

As the Times so properly states:

The plan for broad use of X-ray body scanners to detect bombs or weapons under airline passengers' clothes has rekindled a debate about the safety of delivering small doses of radiation to millions of people — a process some experts say is certain to result in a few additional cancer deaths.

The scanning machines, called "backscatter scanners," deliver a dose of ionizing radiation equivalent to 1 percent or less of the radiation in a dental X-ray. The amount is so small that the risk to an individual is negligible, according to radiation experts. But collectively, the radiation doses from the scanners incrementally increase the risk of fatal cancers among the thousands or millions of travelers who will be exposed, some radiation experts believe.

Indeed the data is lacking. We do not know what the results of such continual assaults on the skins DNA will cause. There are about 2-4 billion melanocytes on a human and there are about 20-50 billion keratinocytes, the typical skin cells. It is the 2-4 billion melanocytes we are worried about. Many of them may already be primed for cancer from prior hits.

Also the issue here is that x-ray backscatter is designed to backscatter off the skin, it is not meant to go through, thus it is optimally designed to hit a melanocyte as a target.

The Times continues:

In a 2002 report on the safety of backscatter scanners, the National Council on Radiation Protection and Measurements, which is highly influential in setting regulatory standards, said it "cannot exclude the possibility of a fatal cancer attributable to radiation in a very large population of people exposed to very low doses of radiation."

One author of that report, David J. Brenner, a professor of radiation biophysics at Columbia and director of the university's Center for Radiological Research, said that risk might be increased as the transportation agency moves from using the scanning machines as a second-round check after metal detectors and hand searches to using them as a first-line screening system.

"When we were looking at these a few years back, it was always going to be as a secondary screening tool," he said. "In that scenario, I don't think there's too much concern." But, he said, if millions or tens of millions of passengers a year were scanned with the backscatter X-ray, he said, the risk would be higher.

The problem with all of these studies is that today we know a great deal more about the pathways associated with cancer generation. The Vogelstein model of colon cancer has now been adapted for many other forms of cancers, but there are yet to be filled in gaps. Cancers start with hits to one gene and then another. It may take 2 or even ten hits to genes before a metastatic cancer starts. However many people are genetically prone to have cancer because their genes have been primed by hits at birth. Thus it just takes a few more.

The argument made by the manufacturers is that this it is akin to the radiation on a flight. But that radiation on a flight is gamma rays not x-rays, and not x-rays aimed to scan your skin, skin deep. That is where the melanocytes are.

Frankly in my experience with radiologists, their safety standards are in many cases developed in a gross body manner and not at the molecular level. We know about the pathways at the cell level which cause cancer. We do not know everything but we know enough to set out many flashing red signs. There is a gap in our knowledge and starting an international experiment of whole body radiation is rather Mengele like in character.

1.2 REPORT OVERVIEW

This report looks at the elements of what makes up an reasonable analysis of this problem. Specifically we look at:

1. X-Ray Generation, Detection, and Operations: We provide an overview of x-rays and their generation and properties. This section provides a framework for understanding what issues should be examined in a backscatter analysis. Unlike whole body penetrating radiation, backscatter only penetrates a small portion of the body, at most the outer 1cm depth. Why is this an issue, well simply because when they perform a dosage analysis they assume a total body and not just the shell. Let us demonstrate as follows. Assume the body is a cylinder of radius r, height h, and uniform density. Now the volume is $\pi r^2 h$. Simple. Now assume we have radiation only on the outer 1 cm depth. Then we have another cylinder or radius R, which is R less 1 cm and we have its volume as $\pi R^2 h$. Now if we assume say 1 rem of whole body for a 2 m tall

male of radius 0.3 m we have the following for skin dosage:

$$D_{skin} = D_{whole\_body} \frac{\pi r^2 h}{\pi (r-R)^2 h}$$

$$= D_{whole\_body} \frac{r^2}{\delta^2}$$

$$= D_{whole\_body} \left[\frac{r}{\delta}\right]^2$$

This if the r is 300 cm and the depth 1 cm, we have a 100,000 increase in local dosage. From the Johns Hopkins APL report they determined a 1.45 µrem per scan. Yet if we phrase that in surface only we get 0.5 rem per scan!

2. Backscatter Full Body Scanning: The backscatter process uses lower power x-rays and looks not at transmission but to the scattered x-rays coming from the surface. The process uses a set of flying spot scanning devices and electronically recreates the image. The result is a grey-scale, it really can be made into any color one wants, image of the human. We review what is publicly know of the TSA systems.

3. Basic Genetics of Melanoma and Pathways: The objective here is to have a simple understanding of the current state of knowledge of melanoma and how if develops and how it survives. It is a very aggressive cancer and is complex in its overall pathway structure. We review the literature and present in such a fashion the different pathways. The key here is to understand that any change in one of these pathway genes during either mitosis or transcription will result in the loss of that pathway and as a result may cause a melanoma. What can cause such a change? Simply the x-rays we show above.

DNA Damage and Likelihood of Cancer: What will these x-rays do to the cells on the surface of the skin? The answer is that we really do not know. However, we spend some time on rational conjectures and posing work that should be done to answer these questions. The National Academy of Sciences has issued a report that on the one hand supports TSA and on the other states that we really do not know enough. We argue that we really do not know enough and that we must do more before we expose so many people.

Current Policy Debate: Finally we examine the current policy debate. It appears that anyone questioning the Government is termed a traitor with blood on their hands. This is from both the left and the right. This issue seems to have lost all frames of rationality. However we believe that it frames the terms for any future Government controlled debate whether it be backscatter or health care.

2 X-RAY GENERATION

We first discuss some basic principles of X ray generation and the physics underlying it. This will be a critical factor in later understanding the issue regarding the ionizing radiation potential. Our approach will be a bit simplistic but will focus on understanding the principle issues which must be included in any such analysis. We have used original source material where possible and have provided a reasonable amount of technical detail.

The principles of x ray generators are similar to what Roentgen did more than a century ago. It is simply having high energy electrons impact certain metals and then having a scatter which release a photon in the x ray range. The continual impact releases more and more photons over a spectrum which yields the continuous x ray spectrum for that emitter. It will be this which we first look at.

2.1 X RAY TUBES

The x-ray tube is a relatively simple device. It is characterized as follows:

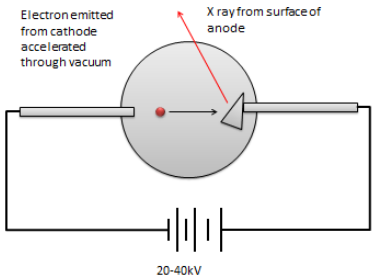
1. A sealed glass enclosure with a high vacuum that ensures that the mean free path for the electrons emitted is sufficiently long so that the electrons go from anode to cathode for collisions. The tube is evacuated to about 10-4 mm of mercury or about 10-7 atm. In this case the mean free path is 50 cm[3].

2. A voltage supply which can provide high enough energy electrons so that collisions are possible and x-ray photons can be released.

3. A cathode material of high enough number so that the outer shell electrons can deflect the incoming electrons and create x-rays.

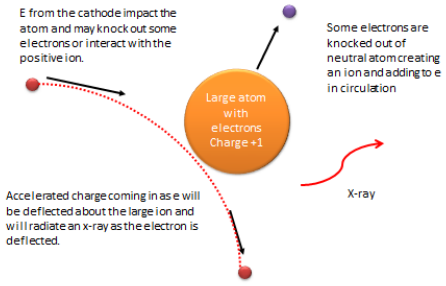
4. Some focusing device which can direct the x-rays generated to a specific location.

The device scheme shown below is an example of such a tube. The x-rays generated



[3] See Sproull, p 7.

Thus the deceleration of the electron as it nears the nucleus of the atom and its rebound from the atom outward results in radiation being emitted. Thus classic theory states that the acceleration will result in emission and quantum theory states that the emission will be a photon. This is the opposite of the classic photoelectric effect, made famous by Einstein. In the photoelectric effect a photon emits an electron, here an electron emits a photon, in the x-ray range of a few A (10E-10 m)[4].



The radiation produced is called Bremsstrahlung radiation, from the German meaning "braking radiation", or the radiation when the electron swings around the positive ion.

2.2 X RAY POWER AND EMISSION SPECTRUM

As the electron goes through the emission of the "braking radiation" the emitted photon will have a maximum frequency or minimum wavelength. This is akin to the same process we see in the photoelectric effect, again a quantum factor. We can determine the wavelength and/or frequency as follows[5]:

$$hf_{max} = eV$$

where

$h = Planck's\ constant$

$e = electron\ charge$

$V = voltage\ across\ the\ gap$

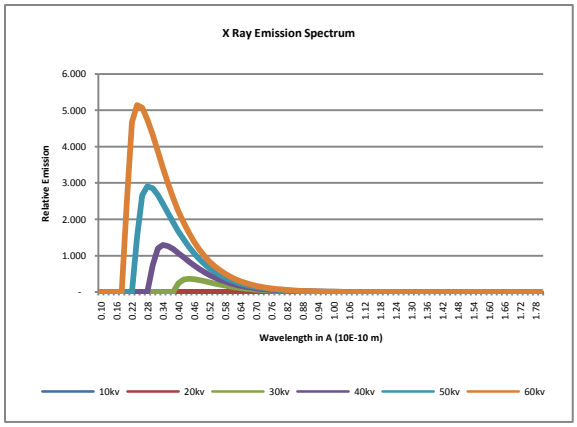
likewise:

$$\frac{hc}{\lambda_{min}} = eV$$

where

$c = velocity\ of\ light$

Now the spectrum of x-ray radiation has a minimum wavelength as defined above and a peak which is directly related to the voltage V. We depict some typical spectral forms as below:



Note that as we increase V we see that the minimal wavelength decreases and that the peak increases. This is called the continuous spectrum. There is also a set of spikes which can occur due to the specific metal at the anode. These spikes are due to deeper electron changes and reflect the quantum structure of these electrons. The line are not of any importance in this analysis.

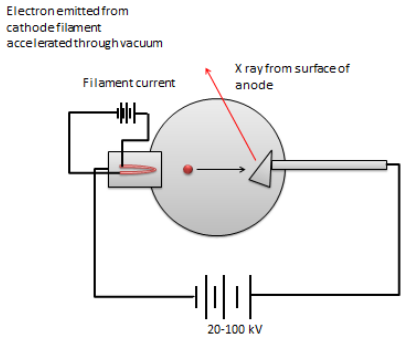
2.3 X RAY CURRENT

The cathode is activated by a high voltage system behind it and in turn the current passing through the cathode is the driver for the electrons emitted. The electrons fly across the gap at a voltage V and impact the anode materials which in turn give off x-ray photons. About 1-5% of the electrons hitting the anode yield an x-ray photon.

The x-rays emitted then are a function of the voltage as we demonstrated above as well as the total current from the cathode to the anode. The next level of detail is shown below. In this tube we have a cathode-anode voltage used for acceleration of V and we have a filament current I. The higher the filament current the more electrons emitted and the more x-rays emitted as well. The high temperature filament is the source of the electrons and the voltage difference between cathode and anode defines the acceleration.

[4] See Alyn pp 100-101.

[5] Sproull (Physics) p. 100-105, Alyn pp 102-103.



As we will discuss later, the TSA system uses a 50 kV x ray device but one cannot ascertain the filament current and thus the electrons emission rate.

Sproull (X Rays) has provided a simple explanation for the emission rate[6]. He proposes the use of the Richardson formula which states:

$$I = AT^{1/2} exp(-b/T)$$

where

$$A = \frac{4\pi mek^2}{h^2} S$$

where

$S = area\ of\ emitting\ surface$

$h = Planck's\ constant$

$T = absolute\ temperature$

$k = Boltzman's\ constant$

$m,e = mass\ and\ charge\ of\ electron$

$$b = \frac{10^7 E_w e}{k}$$

where

$E_w = thermoionic\ work\ function$

Now as Sproull notes:

"The operator of a Coolidge tube soon learns that no appreciable emission of electrons from the filament occurs until it is hot enough to glow brightly. Once the temperature is reached at which measurable current passes between the electrodes, a very slight increase in the filament heating current causes a very great increase in the high-voltage "tube" current carried by the emitted electrons."

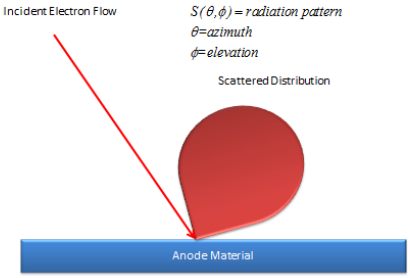
Note that the sensitivity is quite high. Namely there must be substantial control over any x-ray emitter since there can be explosive current growth and thus emitted electron flow and in turn x-ray emissions. This has often been the cause of over exposure on patients and further monitoring of this is quite complex and sophisticated. This alone should be a concern.

Now since:

1 amp is 6.241×10^{18}

we have a conversion efficiency of say 2%, so that we may have $1.2\ 10^{16}$ x-ray photons per second per amp of current from the filament.

The flux coming from the surface of the anode is spatially distributed as well as we depict below:



Thus we must see that the emission under the entire flux emitted will be the 1-5% at best of the incident.

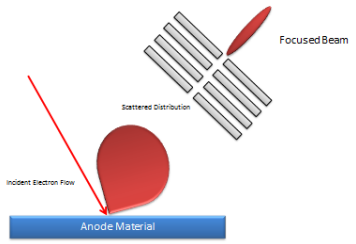
2.4 X RAY FOCUSING AND FLUX

Our final issue regarding the generation of x-rays is the issue of how many x-ray photons are hitting some specific surface area. We will deal with another issue shortly, namely how deep do they go and what are their effects, but we delay that to a later section. Here we are interested in the total flux per unit area, say photons per sec per square cm.

Focusing is generally performed via some form of blockage. The emission pattern from the anode block of say tungsten has a broad pattern and we need to keep it focused. Thus use is made of pin hole non-diffracting focusing devices.

The following depicts a generic focusing system and the ultimate narrowed beam:

[6] Sproull, X Rays pp 11-14.



Now the energy in the focused beam is a fraction of that in the initial beam, and it can be readily calculated using standard techniques as are used in antenna design. For simplicity we can assume we have 10% of the energy focused. Clearly the higher the focus the smaller the energy transmitted.

3 X-RAY DETECTION

Now to detect the x-rays we can either use strong x-rays and have them pass through the person as we do in diagnostic x-ray systems or we can use what are called softer or lower power x-rays which are scattered and not transmitted. Scatter happens all the time, but when we use more powerful x-rays we see the transmitted rays as the stronger and they block out the scattered. The scattered we speak about are the back scattered rays which will shall discuss herein.

3.1 DETECTORS

The detection of x-rays can be by several means. The classic one is the use of film for transmitted x-rays as was seen in medicine for many years. This procedure has been replaced by all digital systems and the detectors are semiconductor and similar devices which respond to incident radiation in the x-ray bands.

As stated by NASA[7]:

This signal can be of three forms. Some detectors, such as proportional counters, CCD (semiconductor) devices, and microchannel plates, measure the electric charge that occurs when the incoming X-ray interacts with the detector's atoms and strips off electrons or causes photo-electrons to be emitted. These electrons can be measured as an electric current, and from this you figure out how much energy the X-ray originally had to create that many electrons. Some detectors, such as scintillators and phosphors, actually measure the light produced when the X-rays interact with the atoms and are absorbed, producing photons (light) in return. Again, measuring the amount of light gives you an idea of how energetic the incoming X-ray was. And some detectors, called calorimeters, do a direct measurement of the heat produced in the material when the incoming X-ray is absorbed.

Thus there are simple CCD, charge coupled device, detectors which measure total incidence, and then scintillators which are akin to photoelectric tubes, and then calorimeters or bolometers which measure energy via secondary physical effects which can be calibrated. The NASA piece continues:

Proportional counters are one of the most common X-ray detectors used by recent missions, although CCD chips are rapidly gaining popularity as the technology improves. Microchannel plates are also a workhorse of satellite missions and continue to be flown today. Calorimeters are a new technology for X-ray measurements, and will be flown on upcoming missions such as Astro-E. Each uses a different approach to detecting incoming X-rays.

A proportional counter is somewhat like a fluorescent light tube in reverse. Instead of applying an electric charge to get light, you let X-ray photons hit it and measure the resulting electric charge. The detector consists of a gas that reacts well to X-rays, in a tube that has electrodes and some applied voltages. The incoming X-ray reacts with the gas, producing electrons through photoionization. These electrons are propelled by the electrode voltage, travel down the detector, and are measured by the electronics at the end.

You can then figure out what the energy of the X-ray was (from the signal strength) and when it hit (from the arrival time and shape of your electronic signal.) You also get some positional information, based on the timing and signal shape. By dividing the proportional counter into smaller cells, you can more accurately determine the position of the incident photon. The most accurate measurement is typically the energy resolution of proportional counters. An advantage is that they also have large surface areas, which means they can capture more incoming X-rays than a smaller detector might, without needing a mirror arrangement to focus X-rays onto them.

Microchannel plates are essentially large X-ray photomultipliers. Made of layers of reactive material divided into narrow channels, these detectors can be made with a good sized surface area, and therefore are good when you want to collect a lot of X-ray photons (without requiring focusing.) Incoming X-rays react within one of the plate glass or metal layers via the photoelectric effect, as with a proportional counter. By measuring the induced signal, and noting the channel location and time of the event, you can get a good measurement of the energy and location of the incoming X-ray. Because they can be made quite large and the technology is relatively immune to distortion by magnetic fields, these large-area detectors have been used on many space missions.

In contrast, a newer technology has become more widespread since the late 1990's. Solid-state detectors like silicon CCDs (Charge-Coupled Devices, similar to the

[7] http://imagine.gsfc.nasa.gov/docs/science/how_l1/xray_detectors.html

CCDs in video cameras) consist of silicon (the standard computer chip material) doped with impurities to create sites where the conductivity is different. Other solid state devices exist, using similar principles as for CCDs.

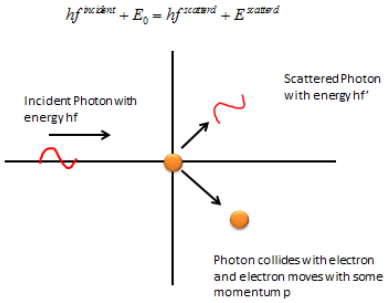
Unlike optical CCDs, which measure light impacting the surface of the chip, X-ray CCDs measure X-rays that penetrate into the middle of the CCD. There, the incoming X-ray creates a cloud of electrons when it reacts with the silicon/impurities, and this cloud is moved (by voltages applied to the chip) in bucket-brigade fashion across the chip and measured at the end as an electric charge.

The charge measurement gives you a very accurate estimate of the energy of the original X-ray. Timing measurements are decent, since you have regular clock-like readouts of your CCD. One issue with CCDs is that they are typically small, and thus have a small collecting area. In other words, you can get very accurate energy measurements, but not as many measurements as a larger detector (like a proportional counter) might. Thus, CCDs work best in situations where you have telescope mirrors to focus X-rays onto them, such as the Chandra X-ray Observatory and XMM-Newton.

The CCD is thus the detector of choice for the backscatter systems.

3.2 COMPTON SCATTERING

The scattering of x-rays is done with Compton scattering, a scattering which accounts for the appropriate quantum effects.



Now we look at Compton scattering in a simple manner following Allyn. We assume the following:

1. An incident photon is incident upon a large particle of some type and this particle has some initial energy state.

2. The photon and particle react and the photon is "scattered". The problem here is that the incident photon has an energy as does the initial state of the particle and the energy is to remain constant. Thus the particle gains some energy and the photon loses some. In fact the photon is annihilated and a new one created at the collision with less energy, a longer wavelength and lesser frequency.

3. If one breaks up the energy balance in x and y coordinated and assumes a scattering angle of θ then we can show by some minor algebra that the change in wavelength is given by:

$$\lambda_{reflected} - \lambda_{incident} = \frac{h}{m_0 c}(1 - \cos\theta)$$

$$h = Planck's\ constant$$

$$m_0 = rest\ mass\ of\ particle$$

This is the Compton equation. We can see that this will be important when we scan the object using the backscatter technique.

We can also show:

$$K = E - E = hf - hf$$

$$and:$$

$$K = hf\frac{\Delta\lambda}{\lambda + \Delta\lambda}$$

$$where\ \lambda\ depends\ on\ the\ scattering\ angle,$$

$$and\ we\ measure\ energy\ of\ photon.$$

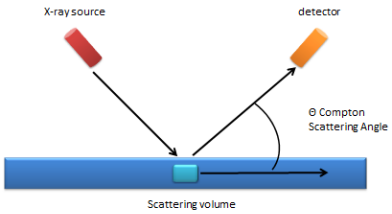
3.3 KLEIN-NISHIMA FORMULA

When scattering from a collections of atoms on the surface, and near to the surface, the return signal is complex. It includes many scatters and depending on the molecules involved may have a complex return profile. That is in essence why Compton backscatter systems work. On the one hand the x-ray is weak and will not go through the person but on the other is powerful enough to backscatter off the top layers of the clothes and skin. That also is the basis of any concern since it is the epidermis and dermis which absorbs all of the radiation.

In this section we summarize the Klein-Nishima formula for backscatter off of a collection of similar molecules. Remember that the beam is spot scanned across the surface being scanned, the radiator is itself a flying spot scanner and the sensors are fixed but sampled according to the Compton angles. From the cumulative signal an image is reconstructed.

We follow the analysis of Rebuffel et al in our presentation[8].

[8] See also Singhai and Burns, as well as the early discussion by Sproull (X Rays).



Now the number of x-ray photons reflected back, scattered back, is given by the Klein-Nishima formula as follows:

$$dN(\theta) = N_{incident} \frac{d\sigma_{KN}(E_0,\theta)}{d\Omega} d\omega n_e dl$$

where

$N_{incident}$ *= number incident photons*

n_e *= volumic density of electrons in material* ($n_e = \frac{N_0 Z \rho}{M}$)

N_0 *= Avrogadro's number*

ρ*=density*

Z*=numnber electrons per nuclide*

M*=molar mass*

And we also have for the scattering cross section:

$$\frac{d\sigma_{KN}(E_0,\theta)}{d\Omega} = \frac{r_e^2}{2}\left[\frac{E_\theta}{E_0}\right]^2\left[\frac{E_\theta}{E_0} + \frac{E_0}{E_\theta} - sin^2\theta\right]$$

where

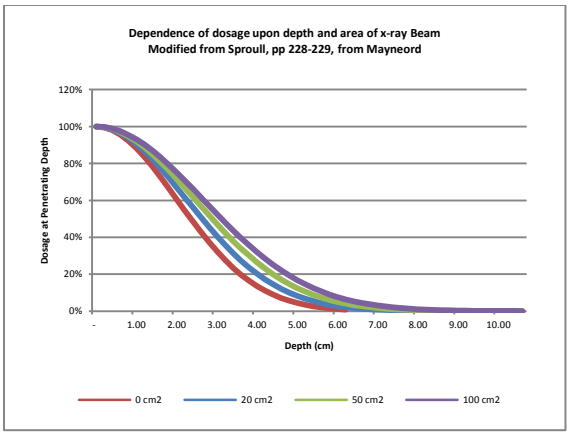
r_e *= classical electron radius*

E_0*=energy of scattered photons*

Thus the signal received reflects the material scattered from to a depth determined by the energy of the x-ray incident beam.

3.4 PENETRATION

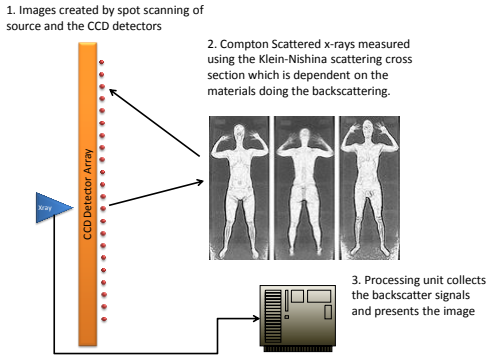
The penetration of x-rays into an absorbing surface also has characteristic which we look for. The plot below depicts some typical early data on the topic. The question is how deep? The answer is not very, namely most of the energy is absorbed in the top few cm. That is where the majority of the skin cells are. Thus we argue that there can be a high flux of x-rays and they impact the top layers of the skin and thus the damage from backscatter should be examined there.



3.5 IMAGE FORMATION

Now the image is formed by processing the reruns from the spot scanner according to the above formulation and then projecting a grey screen image using standardized reflections and achieving reasonably large scale grey image intensity differentials. 64 bit grey scale may be used or higher depending on the desired resolution.

We demonstrate this idea conceptually below.



Thus what happens most likely is as follows:

1. A small spot beam from the x-ray source, focused and operating at 50 kV with an unspecified current level, creates an x-ray beam which is focused and made into a spot. The diameter of the spot on the human is inversely proportional to the scanning time. If we assume a three minute scan time, and if we assume a 2 sq m body surface area[9], and we assume a 5 sq cm spot size, then we have a scan time of:

[9] http://en.wikipedia.org/wiki/Body_surface_area

$$T_{scan} = \frac{T_{Total} A_{Total}}{A_{spot}}$$

$$\approx \frac{200\,sec\,5cm^2}{200{,}000cm^2} = 50\mu\,sec/\ spot$$

Now since the scan is basically frontal and back we could see 100µsec per scan.

2. The CCD detection array receives the backscatter signals and the received signals are themselves small fractions of the x-ray flux incident on the human. They are then processed to determine the relative greyness of the spot that was scanned.

3. The totality of the received signals are image processed so as to determine the overall image which is displayed.

3.6 INCIDENT FLUX

We can now perform a simple thought experiment regarding the incident flux. We can also do another experiment regarding the melanocyte count.

Recall we have 1.2 10^{13} x-ray photons per sec per mA from a source, where the mA refers to the filament current.

Recall that we have a beam that is approximately 0.15 of the 4π sq radians on a sphere. Thus roughly we have 0.15/15 of the full sphere emitted, or 1% focusing. It may be greater and could go as high as 10% or 1.5 sq radians.

Now if we assume a 5 sq cm spot and the source is say 0.5 m away, we can determine the sq radians needed for focusing. The we have in sq radians the spot beam of $4\pi(2.5/50)^2$

This yields a focus of 0.024 sq radians. The fraction of the flux received is then (0.024/1.5) or 1.6% of the total emitted. Let us assume 1%. This is a flux of 1.2 10^{11} x-ray photons per second on a spot. But we are on a spot for 100µsec so we have 1.2 10^7 x-ray photons total per spot.

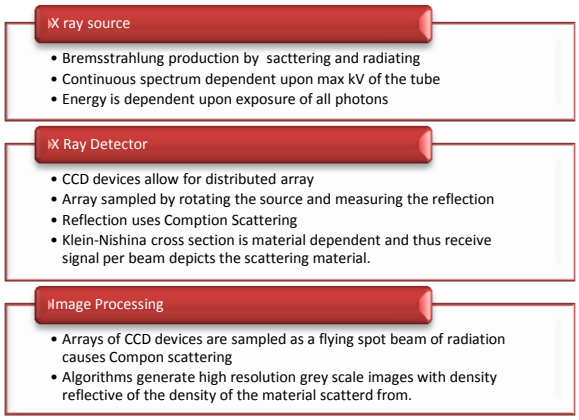
Now regarding melanocytes. There are approximately 2 billion melanocytes on the human body. The human body is about 2 sq m or 200,000 sq cm. Thus there are about 10,000 melanocytes per sq cm. Thus we have 50,000 in a 5 sq cm spot.

Then we have 1.2 10^7 x-ray photons total per spot and 50,000 melanocytes which can be affected by the x-rays. This is the problem.

Now to the beam. There is little available data from TSA. There is a Johns Hopkins APL report but it has been grossly redacted of any information that would useful[10]. Furthermore the APL report focuses on measuring more classic whole body radiation statistics and does not even consider the limits placed by the backscatter approach. The assumptions being classic assume to body in toto absorbs the emitted radiation. Yet as we have shown above with the backscatter it is the top 1 cm of depth the bears the brunt. Nothing of any merit is transmitted, it is all scattered.

4 BACKSCATTER OPERATIONS

The backscatter operations now can be explained simply. We use the following chart as a summary:



4.1 THE APL REPORT

A review of the backscatter system was made available by TSA in a report by Johns Hopkins APL[11]. The basic parameters are simply:

1. X Ray operated at 50 kV

2. Maximum exposure per scan per person: 1.55 µrem

The TSA states:

TSA began deploying state-of-the-art advanced imaging technology in 2007. This technology can detect a wide range of threats to transportation security in a matter of seconds to protect passengers and crews. Imaging technology is an integral part of TSA's effort to continually look for new technologies that help ensure travel remains safe and secure by staying ahead of evolving threats.

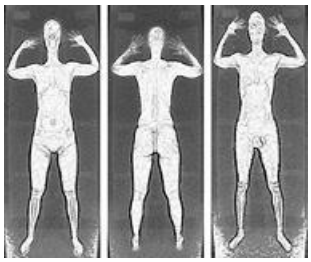
TSA uses two types of imaging technology, millimeter wave and backscatter. Currently, there are 385 imaging technology units at 68 airports.

In March 2010, TSA began deploying 450 advanced imaging technology units, which were purchased with American Recovery and Reinvestment Act (ARRA) funds.

[10] http://www.tsa.gov/assets/pdf/jh_apl_v2.pdf

[11] http://www.tsa.gov/assets/pdf/jh_apl_v2.pdf

Advanced imaging technology screening is safe for all passengers, and the technology meets national health and safety standards.
TSA has implemented strict measures to protect passenger privacy, which is ensured through the anonymity of the image. Additionally, advanced imaging technology screening is optional to all passengers. Learn more about the privacy measures TSA has taken



4.2 ALTERNATIVE VIEWS

There has been some significant negative response from the academic community regarding such backscatter X-Rays and other forms of radiation. They state[12]:

The X-ray dose from these devices has often been compared in the media to the cosmic ray exposure inherent to airplane travel or that of a chest X-ray. However, this comparison is very misleading: both the air travel cosmic ray exposure and chest Xrays have much higher X-ray energies and the health consequences are appropriately understood in terms of the whole body volume dose. In contrast, these new airport scanners are largely depositing their energy into the skin and immediately adjacent tissue, and since this is such a small fraction of body weight/vol, possibly by one to two orders of magnitude, the real dose to the skin is now high.

In addition, it appears that real independent safety data do not exist. A search, ultimately finding top FDA radiation physics staff, suggests that the relevant radiation quantity, the Flux [photons per unit area and time (because this is a scanning device)] has not been characterized. Instead an indirect test (Air Kerma) was made that emphasized the whole body exposure value, and thus it appears that the danger is low when compared to cosmic rays during airplane travel and a chest X-ray dose.

Our colleagues at UCSF, dermatologists and cancer experts, raise specific important concerns:

A) The large population of older travelers, >65 years of age, is particularly at risk from the mutagenic effects of the X-rays based on the known biology of melanocyte aging.

B) A fraction of the female population is especially sensitive to mutagenesisprovoking radiation leading to breast cancer. Notably, because these women, who have defects in DNA repair mechanisms, are particularly prone to cancer, X-ray mammograms are not performed on them. The dose to breast tissue beneath the skin represents a similar risk.

C) Blood (white blood cells) perfusing the skin is also at risk.

D) The population of immunocompromised individuals--HIV and cancer patients (see above) is likely to be at risk for cancer induction by the high skin dose.

E) The risk of radiation emission to children and adolescents does not appear to have been fully evaluated.

F) The policy towards pregnant women needs to be defined once the theoretical risks to the fetus are determined.

G) Because of the proximity of the testicles to skin, this tissue is at risk for sperm mutagenesis.

H) Have the effects of the radiation on the cornea and thymus been determined?

Moreover, there are a number of 'red flags' related to the hardware itself. Because this device can scan a human in a few seconds, the X-ray beam is very intense. Any glitch in power at any point in the hardware (or more importantly in software) that stops the device could cause an intense radiation dose to a single spot on the skin. Who will oversee problems with overall dose after repair or software problems? The TSA is already complaining about resolution limitations; who will keep the manufacturers and/or TSA from just raising the dose, an easy way to improve signal-to-noise and get higher resolution? Lastly, given the recent incident (on December 25th), how do we know whether the manufacturer or TSA, seeking higher resolution, will scan the groin area more slowly leading to a much higher total dose?

We are unanimous in believing that the potential health consequences need to be rigorously studied before these scanners are adopted. Modifications that reduce radiation exposure need to be explored as soon as possible.

This letter was strongly rejected by FDA staff, despite for example the APL report. The FDA staff latter to the Presidential Scientific Advisor is chilling. The Advisor seems to have just pushed the paper from one desk to another. Perhaps there should be some disinterested analysis.

5 SKIN AND MELANOMA

We now will look at the skin and the melanocyte and then examine the pathways which control melanocyte growth. Melanoma is a growing issue for individuals. As Rigel et al state[13]:

[12] http://www.whitehouse.gov/sites/default/files/microsites/ostp/ucsf-jph-letter.pdf

[13] http://caonline.amcancersoc.org/cgi/content/full/caac.20074v1

Melanoma is an increasingly important public health problem in the United States and worldwide. The incidence of melanoma has been increasing faster than that of any other cancer in the United States. Overall, melanoma incidence increased at an average of 4.6% annually from 1975 to 1985 and 2.7% annually from 1986 to 2007. Statistically significant increases are occurring for tumors of all histologic subtypes and thicknesses, including those greater than 4 mm. Invasive melanoma currently is the fifth most frequently diagnosed cancer in men and the sixth most frequently diagnosed cancer in women in the United States. In 2010, 68,130 newly diagnosed cases of invasive melanoma and 46,770 cases of in situ melanoma are expected. At current rates, the lifetime risk of an American developing invasive melanoma is approximately 1 in 58 overall and 1 in 39 for Caucasian men and 1 in 58 in Caucasian women. This contrasts dramatically with a lifetime risk of 1 in 1500 for Americans born in 1935.[4] *Approximately 8700 people are expected to die from melanoma in the United States during 2010, accounting for 65% of all skin cancer deaths.*

Thus as regards to x-rays and their ionizing effects it is essential to have a modicum of understanding of this cancer. This understanding must be able to go down to the cellular level including the molecular pathways as well as the specifics of cell growth and the normal transcription process of DNA.

5.1 SKIN ANATOMY

The skin is the largest organ of the body. A skin cell is about 30 µm in diameter and the top layer of the skin, the epidermis, may be 5 to 15 cells thick and this 150 to 450 µm in thickness, about 0.5 mm at the deepest. The skin is composed of:

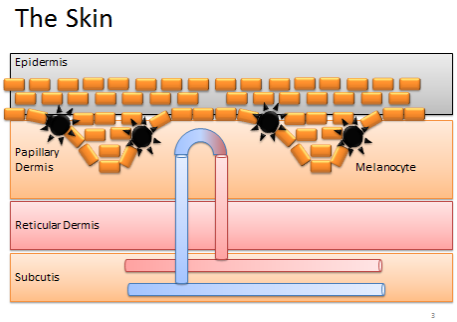
1. Keratinocytes, the most abundant cells, which are always growing and migrating upward where they die off and fall off the person. The tow very top layers are the stratum corneum at the very outermost surface and then just below that is the stratum granulosom, the layer of dying keratinocytes.

2. Langerhans cells (4% of total):

3. Merkel cells (<1% of total):

4. Melanocytes (3% of the total): The melanocytes remain at the basal layer of the epidermis and have long tentacles which spread upward to the upper layers and from these tentacles they emit the melanocytes, the pigment of the skin and the general pigment of a nevus. Any movement, up or down, from the basal layer, of the melanocytes is pathognomonic of a malignancy of some form. Stability of the melanocyte is the sine qua non of a benign cell. Unlike the keratinocytes, which are reproducing and dying, the melanocytes are generally non-reproductive and stable. Their major function is to produce melanosomes.

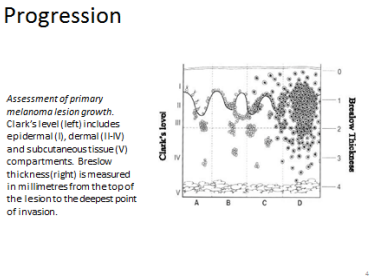
The figure below depicts the characteristics of the skin. The papillary dermis is about 0.4 to 0.6 mm in thickness and contains blood flow both from below and within the layer itself. It abuts the epidermis. It is composed of many collagen fibers and blood and never fibers.



5.2 MELANOMA AND PRE-DISPOSITIONS

Melanoma is a very aggressive cancer and it is found I various forms. However the most common is superficial spreading melanoma which is a vertically spreading form before it develops a vertical spread and metastasizes. In contrast there is nodule melanoma and excessively aggressive form which starts with vertical spread and then attacks many organs. There currently is limited approaches with dealing with melanoma other than initial excision. Melanoma in situ is defined as melanocytes leaving their basal layer and moving into the upper portion of the epidermis. If excised there is a 100% cure rate for MIS. However if the melanocytes migrate downward and outward we then have the potential for deadly spreading melanoma and the cure rate drops accordingly.

The following shows the progression of melanoma:



Now the question is where does this come from; genetic, environmental, or what? There are a few genetic related causes. However, there are also predisposing conditions such as a dysplastic nevus syndrome which one can see raises the chance of the nevus becoming malignant. We will use the excellent overview by Dr. Ossia-Margarita Rosemarie Eichhoff in her thesis at Zurich to present the summary of these issues[14]. There are familial predispositions in some cases. Eichhoff states:

[14] http://e-collection.ethbib.ethz.ch/eserv/eth:1923/eth-1923-02.pdf

*A family history of the disease is identified in 10% of all melanoma cases …**The risk for individuals with a family history to develop metastatic melanoma is increased if there are multiple cases of melanoma in the family, multiple primary melanomas in a family member or early onset of disease in a family member**. Chromosomal analyses of melanoma-prone families have identified **two high-risk loci**. One is located at **9p21** and encodes the **CDKN2A** gene locus … Various mutations at 9p21 have been found in about half of all melanoma-prone families …. The absence of the mutation in other melanoma-prone families indicates the existence of other tumor suppressor loci not yet identified (Lesueur et al, 2008). The estimated worldwide penetrance for mutation carriers in CDKN2A is 30% by the age of 50 and 67% by the age of 8…*

***Another melanoma risk gene is located at 12p14** and encodes cyclin-dependent kinase 4 (**CDK4**… Only three families have been reported to carry mutations of CDK4 worldwide. Interestingly, all mutations occur in codon 24 … which is critical for Cdk4 binding to p16 (a CDKN2A locus gene product). Since the activities of Cdk4 and p16 both affect the same downstream effectors, it is not surprising that CDKN2A mutation-positive and CDK4 mutation-positive families present similar clinical characteristics …*

Thus there are at present just two recognized genetic predispositions for familial melanoma.

1. 12p4 encoding for CDK4
2. 9p21 encoding for CDKN2A

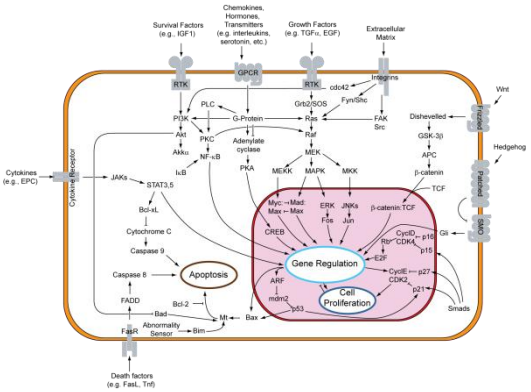
both being kinases.

5.3 MELANOMA PATHWAYS

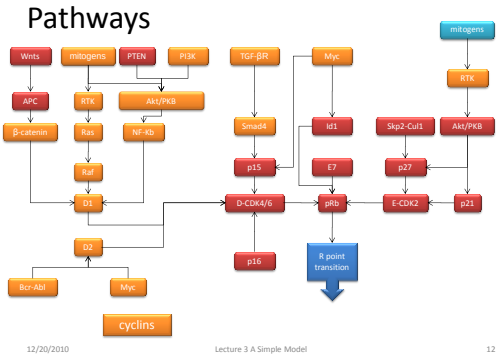
We will now look at several specific genetic control paths and the ways in which their changes and alterations result in melanoma[15]. There are many such elements and pathways for many different cancers but we shall focus specifically on the one for prostate cancer. The Table below depicts a summary of prostate cancer impacting genes and genetic pathways. One must remember, however, the analysis of Dougherty, when looking at this Table. Just because a gene is present and expressing or absent and not expressing, one must understand the link of causality and not just the existence to draw complete conclusions.

5.4 BASIC PATHWAYS

The following is a description of some of the many of the pathways found to be active in cancer cells[16]:



We can also look at some of these pathways in smaller detail as follows:



The R point transition control relates to the mitotic pathway a key to malignant growth. Many of these elements have been identified in the development of melanomas.

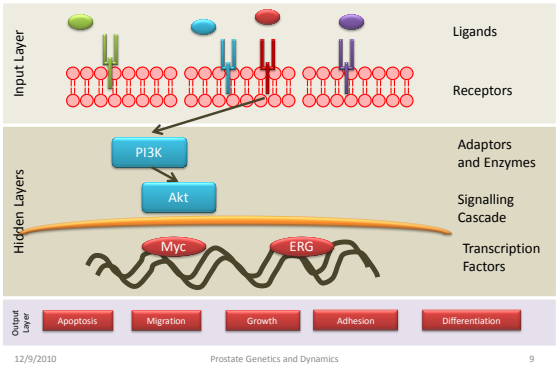
Pathways are a critical and fundamental issue regarding the homeostasis of cells. The elements in the pathways above are for the most part proteins derived from genes in the cell. If the genes are as they should be then the genes do what they should do, namely carefully fulfill its role. If, however, the gene has mutated for some reason, then the gene product may be changed and further the change may elicit additional changes. As we shall discuss later, changes may occur during the replication of the cell or during the basic process of transcription, going from DNA to RNA. In an ionizing environment, simple changes such as the switching of a single base pair resulting from some ionization may result in a change.

The following is from Weinberg and provides a good descriptive of what the elements in these pathways control. They deal with apoptosis or natural cell death, migration, growth, adhesion, and differentiation. Normal cells as they develop become good for one functional purpose within a single organ. Cancer cells have no productive purpose and just go everywhere eating up the environments where they land.

[15] There are many papers in this evolving field. The one by Bennett is also useful as a current update. There appears to be no generally accepted consensus as to what the ultimate pathways are. In fact this is a common issue across many cancers except a few, colon cancer being the most well understood on the pathway basis.

[16] http://en.wikipedia.org/wiki/File:Signal_transduction_v1.png

Structure (from Weinberg p 120)



Before we discuss the possible changes, we will look at the key pathway elements as they are involved in melanoma. The very same pathway elements are involved in other cancers so what we are saying here for melanoma can apply in part for prostate cancer as well.

5.5 SPECIFIC PATHWAYS

Current research looks at the pathways and their aberrations for understanding what can happen in a normal melanocyte which would drive it to a cancerous state. We summarize referring to the thesis of Weinberg:

5.5.1 MAPK

*Somatic mutation of genes involved in the **mitogen activated protein kinase** (MAPK) pathway has been identified in a large proportion of melanoma cell lines and tumours. In normal tissues the MAPK pathway responds to cytokine activity by regulating cell growth, survival and migration via the transmission of a series of phosphorylation events to the nucleus. Extracellular signals are transduced through receptor tyrosine kinases (RTKs) by small membrane bound GTPases called RAS, which in turn activate a phosphorylation cascade of cytosolic kinases including RAF, MEK1/2 and ERK. Cytokine-mediated stimulation involves a diverse variety of RTKs such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-kit and fibroblast growth factor receptor (FGFR). The hyper activation of these factors is frequently observed in a variety of cancers including melanoma.*

5.5.2 RAS and RAF and BRAF

The following is a summary of the RAF genes:

ABL1 (ABL)	Translocation	Chronic myelogenous leukemia	RTK
ALK	Translocation	Anaplastic large cell lymphoma	RTK
BRAF	Activating codon change	Melanoma, colorectal, thyroid	RTK
EGFR	Amplification, activating codon change	Glioblastomas, non–small cell lung cancers	RTK
EPHB2	Inactivating codon change	Prostate	RTK
ERBB2	Amplification	Breast, ovarian	RTK
FES	Activating codon change	Colon	RTK

We look particularly at B-RAF which is frequently found in melanomas.

*The **RAS downstream target v-raf** murine sarcoma viral oncogene homologue B1 (**BRAF**) is mutated in 50-80% of melanomas most commonly with a single substitution (V600E) in its kinase domain. Kinase activity is regulated by the phosphorylation of T599 and S602 residues within the activation segment. Mutation of the valine at position 600 to a glutamate residue is thought to mimic the activating phosphorylation event and results in constitutive activation of the kinase. Since the BRAF^{V600E} mutation is the most common in melanoma, it highlights the importance of the MAPK pathway regulation in melanocytic.*

Interestingly, 80% of benign nevi also express BRAF^{V600E}, and it has been demonstrated in nevi that expression of BRAF^{V600E} drives senescence. This suggests that other control mechanisms are acting with the MAPK pathway in a cell context-dependent manner in order to regulate cell cycle checkpoints.

*Along with this finding it has been shown that the **incidence of mutated BRAF is high in vertical growth phase (VGP) melanoma but low in radial growth phase (RGP) melanoma** . Therefore, BRAF mutations alone are unlikely to be involved in the initiation of melanoma, but are rather involved in the hyper proliferative processes characteristic of melanocytic lesions. This further supports a cell context-dependency in which additional mutations, for example in Mc1R or PTEN, are necessary to drive malignancy.*

5.5.3 NRAS

*The **neuroblastoma RAS viral oncogene (NRAS)** is a GTPase activated by RTKs. When activated NRAS induces MAPK/ERK phosphorylation to drive cell proliferation. In addition, NRAS is also known to activate phophoinositide-3 kinase (PI3K) which inhibits apoptosis. Therefore, activating mutations in RAS lead to enhanced cell proliferation and survival. One such activating mutation in NRAS (Q61R) occurs most often in melanocytes of sun-damaged skin, with frequencies of 56% in congenital nevi, 33% in primary nevi and 26% in metastatic melanoma. Interestingly, melanomas which show activating RAS mutations lack BRAF mutations and vice-versa, indicating that only one mutation in the MAPK pathway is necessary. It has been shown in mice that introduction of the NRAS (Q61R) mutation in a CDKN2A-deficient background*

promoted melanoma formation and metastasis to lymph nodes and other distal sites with 30% penetrance.

5.5.4 c-KIT

*The **v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene (c-Kit) is a RTK family member** and is activated by a specific cytokine known variously as stem cell factor, mast cell growth factor or Kit ligand. Activating mutations in the receptor's kinase domain increases the secretion of its ligand which in turn increases autocrine activation. It is reported that activation of c-Kit in a physiological setting is responsible for ERK2-dependent phosphorylation of Mitf and recruitment of the p300 transcription co-factor (CREB-binding protein), thus suggesting an important role for c-Kit in Mitf regulation and melanocyte development . Similar to MAPK pathway factors, mutations in c-Kit occur in melanomas derived from sun-damaged skin with a frequency of 28%. However, they also occur in melanomas derived from acral (36%) and mucosal (39%) tissues . Interestingly, c-Kit receptor expression is reported to be down-regulated during melanoma progression and several studies have shown that either re-expression of c-Kit or exposure to stem cell factor in melanoma cell lines leads to their apoptosis. This suggests that the relevance of c-Kit activation to melanoma is more likely in malignant transformation of melanocytes than in disease progression. However this contrasts with the observation that while constitutively activated c-Kit in mice leads to increased melanocyte migration, it does not increase cell proliferation or induce tumourigenic transformation.*

5.5.5 PTEN

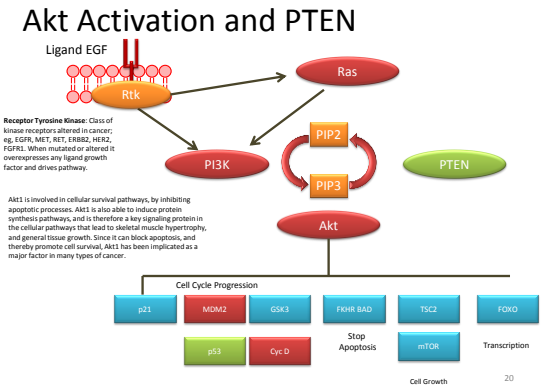
PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a dual-specific phosphatase which can dephosphorylate phosphoserine and phosphotyrosine residues in target proteins (Myers et al, 1997). PTEN also functions as a lipid phosphatase by hydrolysing a phosphate residue in phosphatidylinositol 3,4,5-trisphosphate (PIP3) to produce phosphatidylinositol 4,5-bis phosphate (PIP2).

PIP3 mediates the phosphorylation and activation of serine/threonine protein kinases B (PKBα/β/γ, also known as: AKT1, AKT2, AKT3). By dephosphorylating PIP3 to PIP2 PTEN negatively regulates AKT kinase activity. Several studies have shown that AKT activity regulates the transcription of a wide range of genes, especially those involved in cell proliferation, apoptosis, and cell survival. Moreover it has been demonstrated that loss of PTEN leads to decreased sensitivity to apoptosis through increased phosphorylated AKT . In contrast, forced expression of PTEN induces apoptosis through inhibition of AKT phosphorylation.

Therefore, the loss of PTEN and the activation of RAS are associated in the same pathway within the context of cell survival. The potential interaction between mutations in NRAS, BRAF and PTEN may play a critical role in melanoma development. Loss of PTEN function was detected with frequencies of 30% in melanoma cell lines and 10% in uncultured specimens. PTEN inactivation was found in only 8% of melanocytic nevi, but decreased levels of PTEN were found in 63% of primary melanomas (Tsao et al, 2003b). This indicates that loss of PTEN is related to melanoma progression and initiation. Recently it was demonstrated, in a mouse study performed by Dankort and colleagues, that an activating mutation in BRAF^{V600E} led to the development of benign melanocytic hyperplasia that failed to progress to melanoma.

Strikingly, only the offspring from BRAF^{V600E} mutated and PTEN-deficient mice developed melanoma with 100% penetrance of metastasis to the lymph nodes and lung (Dankort et al, 2009). This data shows how activated BRAF may cooperate with PTEN silencing to promote the development and progression of metastatic melanoma.

PTEN is a critical regulator which when closed down and inactive permits unregulated growth. We show the PTEN pathway in some detail below. Note the loss of PTEN activates Akt which sets in motion a set of other pathways. PTEN is often de-activated in prostate cancer as well as in many melanomas.



5.5.6 APAF1

The apoptotic peptidase activating factor1 (APAF1) is a downstream target of p53 which induces apoptosis by activating caspase-9. In malignant melanoma, about 40% of melanoma lesions show low expression of APAF1 due to loss-of-heterozygosity (LOH) and this inversely correlates with chemosensitivity in melanoma cultures (Fujimoto et al, 2004b; Soengas et al, 2001). Interestingly, loss of APAF1 is more frequently observed in metastatic melanomas than in primary tumours, and indicating that the significance of this factor may be in disease progression and not initiation (Fujimoto et al, 2004a).

5.5.7 WNT

The Wnt signal pathway is an evolutionarily conserved mechanism which is critically involved in both early development and cancer progression. It is currently thought that Wnt signal transduction follows at least three independent routs: the canonical (Wnt/βcatenin), non-

canonical (Wnt/Ca^{2+}) and planar cell polarity (PCP) pathways. The Wnt family of proteins includes at least 19 different secreted factors which activate signaling by binding to Frizzled (Fzd) family receptors and their co-receptors including low-density lipoprotein receptor-related proteins (LRP), orphan tyrosine kinase receptors (ROR) and crypto. In humans, there are ten Fzds and two LRPs acting as receptors for Wnt signaling. This wide variety of Wnt ligands and receptors allows for a range of distinct cellular responses. Activation of Wnt signaling is regulated by a combination of secreted Wnt ligand availability and the expression of appropriate receptors.

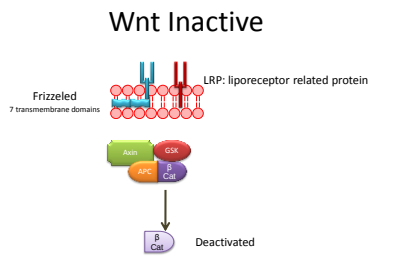
For example, Wnt3a binding to a FZD/LRP receptor complex preferentially activates the canonical Wnt pathway. Alternatively, Wnt5a binding to a FZD/ROR2 receptor complex preferentially activates the non-canonical Wnt pathway. Furthermore, heparin sulphate proteoglycans (HSPGs) present on the cell surface and in the extracellular matrix are thought to play a role in stabilization and presentation of Wnt ligands to their receptors. This suggests that HSPG expression and glycosylation play an important role in mediating Wnt signal transduction. Finally, actin-based filopodia extension and cytoskeleton dynamics have also been shown to both influence and be dependent on Wnt signaling, thus regulating cell morphology and motility . There is also evidence for cross-talk between Wnt signaling and other pathways, including transforming growth factor-beta (TGF-β) and mitogen-activated protein kinase (MAPK) pathways.

Mutations in components of Wnt signaling are known to lead to various developmental defects. Similarly, in cancer the deregulation or hyper-activation of Wnt signaling is widely reported to drive tumor cell proliferation and metastatic progression . The following sections discuss the canonical and non-canonical Wnt pathways as well as their roles in cell-cell adhesion and motility during both melanocyte and melanoma development.

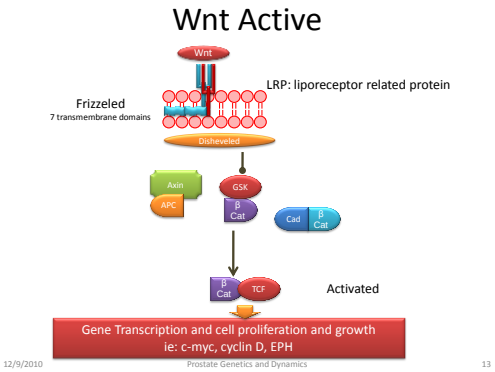
To summarize, we can say this of Wnt[17]:

- The **canonical Wnt pathway** describes a series of events that occur when Wnt proteins bind to cell-surface receptors of the Frizzled family, causing the receptors to activate Dishevelled family proteins and ultimately resulting in a change in the amount of β-catenin that reaches the nucleus
- Dishevelled (DSH) is a key component of a membrane-associated Wnt receptor complex which, when activated by Wnt binding, inhibits a second complex of proteins that includes axin, GSK-3, and the protein APC
- The axin/GSK-3/APC complex normally promotes the proteolytic degradation of the β-catenin intracellular signaling molecule.
- After this "β-catenin destruction complex" is inhibited, a pool of cytoplasmic β-catenin stabilizes, and some β-catenin is able to enter the nucleus and interact with TCF/LEF family transcription factors to promote specific gene expression

Wnt also has several ways of acting. We show two here:



and when activated the following occurs:



The activation by Wnt results in cell proliferation and growth, and is often unregulated.

In another Zurich researchers thesis, Dr. Natalie Schlegel**,** it states:[18]

We contend that melanoma cells switch between two defined gene expression signatures, each underlying a distinct cell phenotype, which together drive disease progression. Presented in this thesis are the in vitro and in vivo experimental validations for this model, the investigation of the role of TGF-ß-like signalling, predominantly its role in growth inhibition, and the identification of Id2 as a gene involved in TGF-ß-induced growth inhibition response. After a literature review of genes identified to have phenotype-specific expression, we identified Wnt and TGF-ß signalling as drivers of the identified transcriptional signatures. By in vitro characterization of phenotypically opposed cells, we

[17] This comes from the "wingless" gene and thus the Wn prefex. The was related to discovery on fruitflies.

[18] http://e-collection.ethbib.ethz.ch/eserv/eth:30488/eth-30488-01.pdf

identified the two phenotypes as proliferative and invasive. As well as showing divergent proliferative and invasive behavior, cell types could be discriminated based on their growth susceptibility to TGF-ß and their capacity for vasculogenic mimicry.

Reduced susceptibility to the growth inhibiting effects of TGF-ß and the capacity for vasculogenic mimicry have both been associated with increased invasive and metastatic properties of melanoma cells. Our model suggests that both proliferative and invasive transcriptional signatures are important in disease progression and that each melanoma cell retains the capacity to express either signature given appropriate signalling. Our model also accounts for much observed gene expression heterogeneity in melanoma tumours.

This heterogeneity and reversibility of transcription programs were also shown in vivo using a xenograft mouse model. We also investigated the motive forces behind differential TGF-ß signalling. Smad activation was present in all melanoma cultures irrespective of the presence of a TGF-ß signature, which suggested Smad-independent TGF-ß signalling. The TGF-ß Smad-dependent pathway has long been considered as being central to TGF-ß signalling but it is now recognized that TGF-ß signals via crosstalk with alternative pathways. We investigated alternative pathways but could identify no link between the activation status of several MAPK pathways and the TGF-ß signature. TGF-ß is a multifunctional cytokine which controls aspects of cell proliferation, differentiation, migration, apoptosis, adhesion, angiogenesis, immune surveillance, and survival. TGF-ß was initially defined as a transforming cytokine but it is now understood that TGF-ß has dual roles both as tumor suppressor and tumor promoter.

To better understand the regulation behind the expression of these opposite behaviors, we studied TGF-ß's cytostatic effect, which plays an important role in its tumor suppressing function and which is lost as melanoma cells become more invasive and metastatic. We identified the Id2 gene as differentially regulated by TGF-ß and link the loss of its regulation to acquired resistance to TGF-ß in invasive phenotype cells. We show that TGF-ß induces cell cycle arrest through induction of pI5fnk4b and repression of Id2. Furthermore, Id2 overexpression in proliferative phenotype cells counteracts pI5fnk4b induction and consequently protects melanoma cells from TGF-ß-mediated inhibition of proliferation.

Treating tumours comprised of cells with variably expressing transcription signatures presents a difficult challenge. This is because specific therapies have targeted factors we identify here as being subject to repeated changes in regulation. It is therefore of primary importance we recognize that the existing paradigm for melanoma progression is insufficient for the design of effective therapies.

5.6 PATHWAY SUMMARIES

An excellent summary is also in DeVita, in the chapter by Fisher and Kwong. We first summarize this in the following Table using the materials in the Fisher and Kwong chapter:

Gene	Action
AKT	The AKT gene family consists of AKT1, AKT2, and AKT3, with phospho-AKT as the read out of their overall activation status. Elevated phospho-AKT level was reported to be adversely associated with patient survival.32 More recently, copy number gains of the AKT3 locus were detected in melanomas, suggesting that the AKT signaling point itself may be oncogenic. Interestingly, targeted depletion of AKT3 could trigger apoptosis,33 while AKT1 behaved as a tumor suppressor in melanoma cell lines,34 pointing to poorly understood distinct and overlapping functions of these related family members.
APAF-1	Allelic loss at 12q23 was exhibited by 10 of 24 (42%) melanomas in a study,16 with the common area of loss focused on the APAF-1 locus. LOH correlated tightly with a reduction in Apaf-1 protein levels, as judged by immunohistochemistry. Although no mutations were detected, the loss of expression was determined to be due to silencing in a methylation-dependent manner.
ARF	Reciprocal to the *INK4A*-specific human mutations, *ARF*-specific insertions, deletions, and splice donor mutations have been described in human melanomas (reviewed in Chin et al.14). However, in these cases, either the maintenance of INK4A function or true ARF inactivation was not shown, making it ambiguous whether the genetic disruption of ARF alone is sufficient for tumorigenesis.
BRAF	Somatic activating BRAF mutations are found at high frequency in human melanoma, dominated by a single species of point mutation (T →A nucleotide change), resulting in a valine to glutamate amino acid substitution (V600E). Although the T→A transversion is not classically associated with UV-induced damage, BRAF mutations appear to be more common in melanomas arising on sites with intermittent exposure to UV.23,24 However, melanomas from chronically sun-damaged skin are typically wild type for *BRAF*,
CDK4A	*CDK4* is a direct target of inhibition by p16INK4A (Fig. 48.1.2) and is a primary regulator of RB activation. If INK4A acts mainly through the RB pathway, it would be predicted that activating CDK4 mutations could functionally substitute for INK4A deletions. Indeed, rare germline mutations of *CDK4* that render the protein insensitive to inhibition by INK4A have been identified in melanoma-prone kindred.8 Somatically, these tumors retain wild-type INK4A function, suggesting that INK4A is epistatic to CDK4 and that Rb pathway deregulation is central to melanomagenesis.
CDKN2A	Its importance is explained in part by its unusual organization, which allows for two separate transcripts and corresponding tumor suppressor gene products to be produced: p16INK4A and p19ARF (Fig. 48.1.2). Loss of p16INK4A results in the suppression of retinoblastoma (RB) activity via increased activation of the CDK4/6-cyclin D1 complex; loss of ARF (p14ARF in human and p19ARF in mouse) results in the suppression of p53 activity through increased activation of MDM2. Thus, deletion of the entire locus accomplishes the inactivation of two critical tumor suppressor pathways: RB and p53.
c-MET	The c-MET gene product and its ligand hepatocyte growth factor/scatter factor (HGF/SF) are known to activate the MAPK pathway, but have many additional functions. It has long been documented in the literature that overexpression of c-MET and HGF is correlated with melanoma progression, with nonfocal amplification of the c-MET locus at 7q33-qter being associated with invasive and metastatic cancers in humans46 and their high levels of expression in murine melanoma cell lines being similarly correlated with metastatic ability in explants.
EGFR	Epidermal growth factor receptor (EGFR) is involved in a complex regulatory loop with the MAPK pathway, where there appears to be bidirectional signaling between EGFR and the RAS kinases. In melanomas, copy number gain of chromosome 7 is linked with overexpression of EGFR, despite the lack of focal amplifications.42 Functionally, although *in vitro* activation of EGFR does not affect melanoma growth, it increased the number of visceral metastases when implanted in severe combined immunodeficiency (SCID) mice.43 Confirmation of EGFR-MAPK cross-talk in melanoma was demonstrated in the inducible H-RAS-driven mouse model,22 where transcriptomic analysis revealed the up-regulation of EGF family ligands including amphiregulin and epiregulin.
INK4A	Human intragenic mutations of *INK4A* that do not affect the *ARF* coding region sensitize germline carriers to the development of melanomas.6 These aberrations can affect the coding region (e.g., exon 1α), either of the 5′ or 3′ untranslated regions (UTRs), the promoter, or splice donor/acceptor sites (reviewed in Sharpless7). This sufficiency of p16INK4A loss for the initiation of melanoma demonstrates that loss of the entire CDKN2A locus is not necessary. In a mouse model engineered to be deficient only for Ink4a (with intact ARF), melanomas formation was observed in cooperation with an oncogenic initiating event (e.g., activated

	H-RAS), albeit with a longer latency than in mice with deletions affecting the entire locus.
MAPK	The MAP kinase (MAPK) pathway contains some of the earliest elucidated human oncogenes, and subsequent analysis of their mechanisms of action unearthed a prevalence of activating mutations across a wide spectrum of tumor types. The focal point of MAPK activation is the ERK1/2 kinases, which classically mediate the transcription of genes involved in cell proliferation and survival (Fig. 48.1.3), but which have also been shown to regulate differentiation and senescence. In addition, the RAS family of proteins has been shown to feed into the PI3K pathway.
MITF	MITF is a gene critical to the survival of normal melanocytes, and identification of MITF as a central modifier of melanoma created a novel class of oncogenes (along with androgen receptor) termed " lineage addiction" oncogenes.50 That is, a tumor may "hijack" extant lineage survival mechanisms in the presence of selective pressures to ensure its own propagation.
P53	The p53 pathway is critical in maintaining a cell with a normal genome via a multiplicity of mechanisms, including cell cycle checkpoints, DNA damage repair activation, and the appropriate induction of apoptosis. Its centrality in tumor suppression is evidenced by the high rate of its inactivation in solid tumors, with mutations in the TP53 gene well established to be present in over 50% of all tumors. By contrast, the TP53 locus is rarely mutated in human melanomas (reviewed in Chin12), although loss of p53 in mice does cooperate with activated H-Ras to induce melanomas.13 Similar to the LOH at *Cdkn2a* in mice heterozygous for Ink4a/Arf knockout, mutant Tp53 heterozygotes also lose the wild-type allele somatically in H-RAS-driven melanomas. Thus, while p53 itself is spared in human melanomas, inactivation of its pathway is likely to be critical.
PTEN	Of the PI3K pathway mutations that do occur, loss of chromosome 10q encompassing PTEN tumor suppressor is the most frequent, the caveat being that there is likely additional tumor suppressor(s) resident in this region (see below). PTEN normally effects the down-regulation of phosphorylated AKT via suppression of levels of the second messenger PIP3 (Fig. 48.1.3). In various genetically engineered mice bearing solid tumors, PT EN loss can be analogous to p53 inactivation, in that one or the other can provide the " last straw" of oncogenesis. In melanoma, somatic point mutations and homozygous deletions of PTEN are rare. Although allelic loss of PTEN is observed only in about 20% of melanoma, loss of expression of PTEN is reported to be in the range of 40% of melanoma tumors.
RAS	Increasing evidence shows that the three different members of the RAS family are not functionally redundant, with separable roles not only among different tissue types, but even within the same tissue. Reflecting this is the differential mutation and genomic amplification rates of the RAS family members within melanomas: N-RAS is the most frequently targeted (33% of primary and 26% of metastatic melanoma samples17), followed by H-RAS (mainly in Spitz nevi).18 Despite its high incidence in other cancer types, K-RAS is rarely observed in melanocytic lesions.19 Interestingly, although N-RAS mutations are found in 54% of congenital nevi, they are rare in dysplastic nevi,20 implying a distinct evolutionary path from dysplastic nevi to melanoma.
RB	RB pathway is responsible for preventing cells from incorrectly entering into the cell cycle, and germline heterozygous loss of the *RB1* gene in humans results in the formation of retinoblastoma. The tumor modulating properties of the RB pathway are well established in many solid cancers, and its deregulation in melanoma is no exception, with demonstrable human mutations in *INK4A*, *CDK4*, or *RB1*.
RB1	Finally, germline mutations in RB1 itself have been found to predispose to melanoma in patients who have survived bilateral retinoblastoma.11 These melanomas show a somatic LOH of the remaining wild-type RB1 allele, strongly implying that an intact RB pathway was selected against in the preneoplastic melanocytes. In such patients, the estimates of increased lifetime risk of melanoma range from 4- to 80-fold.
TGF-β	TGF-β family members are active at various stages of human tumors, but its role in melanoma has only recently begun to become clarified. Studies in zebrafish embryos have translated into human data on the role of Nodal in melanomas. Secreted Nodal was shown to be the molecule responsible for zebrafish axial duplications when human melanoma cells were implanted into the embryos. Subsequent immunohistochemical analysis of Nodal in human melanocytes and melanomas showed a significant correlation with tumor progression. Knockdown of Nodal in metastatic cell lines reduced their invasive capacity *in vi tro* and their growth in mouse xenografts.
WNT	WNT signaling has long been implicated in a wide variety of cancers including breast and colorectal. Its activation of downstream transcriptional events has been hypothesized to control lineage commitment and differentiation fates as well as self-renewal properties. Indeed, the WNT pathway has been linked to major developmental decisions in neural crest derivatives, with a differentiation bias toward the melanocytic lineage.

And in comparison from Bennett we have the following summary which relates specifically to melanoma:

Gene	Location	Change	Melanomas % (no of samples) tested)	Data Source (cultured or not)	Also earlier in progression?
APAF1	12q23	Methylation	42 (24)	Uncultured	No. Advanced only
APC	5q21-22	Methylation (+1 mutation)	16 (94)	Both	Not known
BRAF	7q34	Activating mutation	47 (2805)	Both	51% of benign nevi
CDKN2A(p16, ARF)	9p21	Deletion Methylation Mutation (p16) Total	50 (119) 19 (59) 9 (760) 78	Uncultured(higher in cultured)	Known only for mutations: 0% in nevi, 12% in dysplastic nevi
CDKN2B(p15)	9p21	Deletion	36 (74)	Cultured	Not known
CTNNB1(b-catenin)	3p22	Activating mutation	6 (408)	Both	Not known
KIT	4q12	Amplification ± activating mutation	14 (36)	Uncultured	Not known
MITF	3p14	Amplification	10 (119)	Cultured	Not known
MYC	8q24	Amplification	1–40	Uncultured	Not nevi. Most in advanced
NRAS	1p13	Activating mutation	21 (2517)	Both	21% of benign nevi
PTEN	10q23	Mutation Deletion Total	17 (501) 13 (119) 28	Both Cultured	Not known
PTPRD	9p23	Deletion	6 (119)	Cultured	Not known
RB1	13q14	Mutation	6 (67)	Both	Not known
STK11(LKB)	19p13	Mutation	10 (144)	Both	Not known
TBX2	17q23	Amplification	43 (46)	Cultured	Not known
TP53(p53)	17p13	Mutation	9 (232)	Uncultured	Not known

5.7 PATHWAYS AND METHYLATION[19]

The changes in pathways control elements, by loss of an element of by the hyper-activation of one, frequently is related to methylation of cytosine. Methylation is the replacement of a H atom with a CH_3 methyl group on position 5 of cytosine. How does this happen? Also what does it result in? The result is changes in pathway elements and the above discussions relates many of them. The gene is changed and then the pathway disturbed. The result can be a cancer.

How this happens will discuss shortly.

The issue of having a methylation and then change in DNA during transcription has been discussed by Esteller who states:

[19] See the papers by Miranda, Zilberman, Jacobsen, Robertson, Strathdee for a current description of the methylation process and cancer.

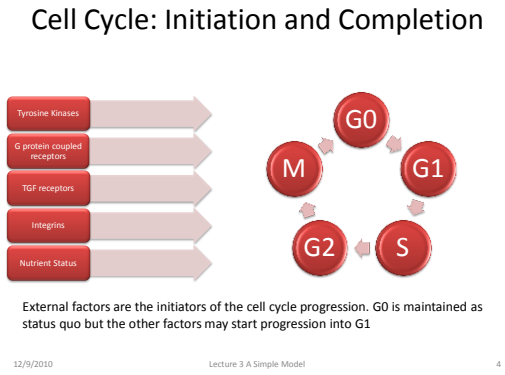
The best-known epigenetic marker is DNA methylation. The initial finding of global hypomethylation of DNA in human tumors5 was soon followed by the identification of hypermethylated tumor-suppressor genes, and then, more recently, the discovery of inactivation of microRNA (miRNA) genes by DNA methylation. These and other demonstrations of how epigenetic changes can modify gene expression have led to human epigenome projects14 and epigenetic therapies.5 Moreover, we now know that DNA methylation occurs in a complex chromatin network and is influenced by the modifications in histone structure that are commonly disrupted in cancer cells... DNA methylation has critical roles in the control of gene activity and the architecture of the nucleus of the cell. In humans, DNA methylation occurs in cytosines that precede guanines; these are called dinucleotide CpGs. CpG sites are not randomly distributed in the genome; instead, there are CpG-rich regions known as CpG islands, which span the 5′ end of the regulatory region of many genes. These islands are usually not methylated in normal cells. The methylation of particular subgroups of promoter CpG islands can, however, be detected in normal tissues.

Esteller continues:

Normally, certain testis specific genes, genes that encode melanoma antigens, or specific proliferation-linked genes38 are silent in somatic cells because promoter-region CpG islands are methylated. In some cancer cells, by contrast, these promoter regions undergo demethylation, and the usually repressed genes become expressed. Two notable examples of the hypomethylation mechanism are the activation of PAX2 (a gene that encodes a transcription factor involved in proliferation and other important activities of cells) and the activation of the let-7a-3 miRNA gene, which has been implicated in endometrial and colon cancer.46,47 The hypomethylation of DNA can have unpredictable effects.

5.8 MELANOMA GENERATION

The question then is what causes the loss of control as we have seen in the previous section. There are two possible routes. First the route of changes that let the pathways start to diverge from homeostasis and the second, most likely resulting in the first, where a change occur in the genetic elements.



One of the key issues then is the deregulation of pathways resulting in loss of control of the normal homeostatic state. As Weinberg states[20]:

"Evidence of an even more cunning strategy for destabilizing this control circuit has been found in the genomes of a small number of both sporadic and familial melanomas. In these cancers, point mutations in the CDK4 gene, the R24C mutation, create CDK4 molecules that are no longer susceptible to inhibition by the family of INK4 molecules (p15, p16, p18, and p19). … CDK needs to be mutated in order for a cancer cell to derive proliferative benefit."

As Bennett states:

Overall, we now know of huge numbers of molecular changes that have been described in advanced melanomas compared with melanocytes. Some commoner and well-known changes are, for example,

- *activating mutations of BRAF …*
- *silencing of E-cadherin expression …, and*
- *acquisition of telomerase activity …*

But hundreds more, mostly unfamiliar, are emerging from comparative gene expression profiling of melanomas from various stages …

What can we make of all these changes? Can we determine which are central to malignancy itself and thus are candidate therapeutic targets? Certainly, we still have much to learn, but as a start, we can seek to distinguish primary from secondary changes.

A primary event in progression would be a cellular change that is clonally inherited, that contributes to the eventual malignancy, and that occurs independently rather than as a secondary result of some other oncogenic change.

These events are either

[20] Weinberg, Cancer, p. 298.

(i) genetic (gene mutation, deletion, amplification or translocation), or

(ii) epigenetic (a heritable change other than in the DNA sequence, generally transcriptional modulation by DNA methylation and ⁄ or by chromatin alterations such as histone modification).

In clonal evolution of cancer, such a primary event would initiate a new, more progressed, clone with a growth advantage over its neighbors, or an alternative selective advantage such as migration …

5.9 SOME SIMPLE CALCULATIONS

We now want to perform a simple calculation. Let us assume methylation is a cause, that is the breaking of a CH bond on cytosine position 5. The question we pose is what causes that and what chance do we have.

We summarize an initial calculation in the following Table. In this Table our objective is to measure the ratio of the x-ray photon energy to the CH bond energy to assure ourselves that we have more than enough energy to break a bond. The details below clearly demonstrate that fact.

CH Bond	99.3	Kcal/mole
Avogadro Number	6.00E+23	
Conversion	2.85	Kcal/mole
Conversion	0.1239	eV/molecule
CH Bond	4.32	eV/molecule
CH Bond width		A
Wavelength of x-ray photon	1.5	A
Wavelength of x-ray photon	1.50E-08	m
Frequency of x-ray photon	2.00E+16	Hz
Energy of x-ray photon	1.33E-17	E=hf Joule
Speed of Light	300,000,000	m/sec
Planck's Constant	6.63E-34	Joule/sec
Conversion	11900	Joule/mole
Conversion	0.1239	eV/molecule
	7.43E+22	Joule/ev
Energy CH bond	5.81E-23	Joule
Energy of x-ray photon	1.33E-17	E=hf Joule
Ratio x-ray Energy to Bond Energy	2.28E+05	

This tells us that the ratio of x-ray energy to CH bond energy is over 100,000 and that the x-ray has an excellent chance to knock off the H and have it replaced by a methyl group.

Calculating probabilities are much more complex and have not been attempted here. The issue here is that we have a flux of x-ray photons and then we have DNA going through many transcription processes. Thus we seek to determine the chance that:

1. An x-ray photon gets to a location to break bonds

2. That the location is also at the time the transcription is occurring.

With regard to total exposures as currently practiced, we have from the paper by Brenner the following Table:

Table 1. Typical Organ Radiation Doses from Various Radiologic Studies.

Study Type	Relevant Organ	Relevant Organ Dose* (mGy or mSv)
Dental radiography	Brain	0.005
Posterior–anterior chest radiography	Lung	0.01
Lateral chest radiography	Lung	0.15
Screening mammography	Breast	3
Adult abdominal CT	Stomach	10
Barium enema	Colon	15
Neonatal abdominal CT	Stomach	20

* The radiation dose, a measure of ionizing energy absorbed per unit of mass, is expressed in grays (Gy) or milligrays (mGy); 1 Gy=1 joule per kilogram. The radiation dose is often expressed as an equivalent dose in sieverts (Sv) or millisieverts (mSv). For x-ray radiation, which is the type used in CT scanners, 1 mSv=1 mGy.

Recall that a 100 rem equals 1 Gy. Thus a neonatal CT would be the equivalent of 2,000 rems.

6 RISK ANALYSIS

We now proceed to look at a risk analysis. Before doing so let us briefly review some facts we have developed:

1. Backscatter radiation uses a 50 kV tube and it also uses a flying spot scant and measures the backscatter, Compton scatter, radiation over a large field and then processes all of the received signal to determine what types of different coverings are on the person based upon the backscatter.

2. The radiation is of short duration, or should be, as the spot goes across the body, so that what is obtained is backscatter and no penetration is achieved. In fact the depth of penetration is on the order of a cm or less.

3. The epidermis is 50 mm thick, and as such bears the full stream of the 50 kV beam, absorbing almost all of the radiation in the first tens of mm of body surface.

4. There are 2 billion melanocytes on the human body and this represent about 2% of all the skin cells, which would in total be 100 billion cells. The melanocytes are continually going through transcription producing a variety of proteins and from time to time go through apoptosis and mitosis or reproduction. Thus given such a large number of cells we will always have some reasonable probability of radiation on a cell during some mitotic event or during some transcription event.

5. The control of the transcriptions and mitotic events in melanocytes is controlled via a complex pathway and also through the effects of micro RNAs which control or modify transcriptions. Most of the pathway elements are believed known and many micro RNAs have been determined also. Thus a reasonable picture of the pathway functioning is

believed to be known at this time. Also most pathway pathologies are also known.

6. The energy of the incident x-ray photon is of a range so that it is possible to interfere with methylation during transcription, or even during mitosis. The exact probability of this can be ascertained if certain experiments are performed. Knowing that probability it is then possible to determine if there will be a methylated change which will result in a pathway change consistent with a melanoma event.

7. Thus any risk analysis must take into account the uniqueness of backscatter as compared to the classic whole body radiation. For the most part, the current practice is focused on whole body radiation, and the very metrics of dosage are whole body directed.

6.1 RISK STUDIES

TSA has performed several risk analyses but for the most part they have been at best perfunctory. Also other professional groups have voiced their views. The following is by ACR the professional organization of Radiologists. They state:

(Originally Posted January 2010)[21] *- Amid concerns regarding terrorists targeting airliners using weapons less detectable by traditional means, the Transportation Security Administration (TSA) is ramping up deployment of whole body scanners at security checkpoints in U.S. airports. These systems produce anatomically accurate images of the body and can detect objects and substances concealed by clothing.*

To date, TSA has deployed two types of scanning systems:

Millimeter wave technology uses low-level radio waves in the millimeter wave spectrum. Two rotating antennae cover the passenger from head to toe with low-level RF energy.

Backscatter technology uses extremely weak X-rays delivering less than 10 microRem of radiation per scan ─ the radiation equivalent one receives inside an aircraft flying for two minutes at 30,000 feet.

An airline passenger flying cross-country is exposed to more radiation from the flight than from screening by one of these devices. ***The National Council on Radiation Protection and Measurement (NCRP) has reported that a traveler would need to experience 100 backscatter scans per year to reach what they classify as a Negligible Individual Dose. The American College of Radiology (ACR) agrees with this conclusion. By these measurements, a traveler would require more than 1,000 such scans in a year to reach the effective dose equal to one standard chest x-ray.***

The ACR is not aware of any evidence that either of the scanning technologies that the TSA is considering would present significant biological effects for passengers screened.

The ACR encourages those interested in learning more regarding radiation associated with imaging and radiation oncology procedures as well as radiation naturally occurring in the Earth's atmosphere to visit www.radiologyinfo.org.

One would not view this as any endorsement. They are not aware of anything to the contrary is not saying that there is no problem. In fact we and the NAS report detail many things which should and must be done to understand the true risks of this technology.

The Health Physics Society states[22]:

The Health Physics Society believes that intentionally exposing people to low levels of ionizing radiation for security screening is justified if certain criteria are met. The key considerations are the net benefit to society and keeping individual doses as low as reasonably achievable (ALARA) while achieving the desired objective. Appropriate organizations should develop criteria for determining when the social benefits of public screening outweigh the risks associated with ionizing radiation exposure. The criteria should represent the consensus of professional, consumer- advocacy, labor, and business organizations; academic institutions; government agencies; and the general public.

The Society's principal recommendations about the practice of security screening individuals by the use of ionizing radiation are:

1. The practice should be limited to those applications that result in an overall net benefit to society.

2. When the practice is used to screen members of the general public, screening systems and their use should conform to the requirements of ANSI/HPS N43.17.1 This Standard limits the reference effective dose2 delivered to the subject to 0.25 microsieverts (25 microrem) per screening. Additionally, a screening facility should not expose any individual to more than 250 microsieverts (25 millirem) reference effective dose in a year.

3. Subjects should be informed of the radiation exposure.

This again is not a ringing endorsement of the technology.

6.2 THE NAS STUDY

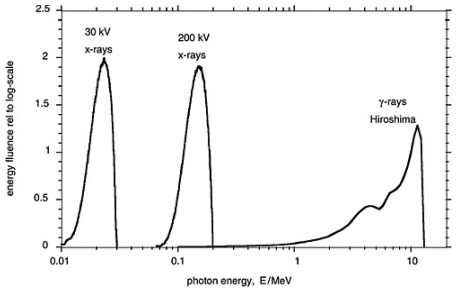
The National Academy states:

[21] http://www.acr.org/SecondaryMainMenuCategories/NewsPublications/FeaturedCategories/CurrentACRNews/archive/StatementonAirportFullbodyScanners.aspx

[22] http://hps.org/documents/securityscreening_ps017-1.pdf

While γ-rays and X-rays of various energies are all sparsely ionizing, in the body they generate electrons with somewhat different spectra of LET values (ICRU 1970). To quantify the differences, reference is usually made to the dose average LET or to the mean values of the related microdosimetric parameter dose-averaged linear energy, y.

The following gives the dose average LET values for the electrons released by monoenergetic photons (solid curves) and compares these values to the averages for 29 kV mammography X-rays and 200 kV X-rays (solid circles and squares, respectively; ICRP 2003). In addition to the dose average, L_D*, of the unrestricted LET, the diagram contains the dose averages,* $L_{D,\Delta}$*, of the restricted LET,* L_Δ*. The restricted LET treats the Δ-rays beyond the specified cutoff energy Δ as separate tracks. This accounts in an approximate way for the increased local energies due to Δ-rays and therefore provides larger values that are more meaningful than those of unrestricted LET.*



Ionizing radiation is known to induce a broad range of potentially mutagenic lesions in DNA ranging from damaged DNA bases to frank DNA breaks and chemically complex lesion clusters. Not unexpectedly, molecular analyses of radiation-induced somatic mutations at a number of loci provide evidence of induction of point mutations in single genes and of small and large deletions that may encompass a number of physically linked genes.

*An important factor in the induction and recovery of deletion-type, multilocus mutations is the degree to which multiple gene loss may be tolerated by the cell. There is good evidence that such tolerance is highly dependent on the genetic context of the mutation (*i.e.*, its position in respect to essential genes and, for autosomal loci, the genetic status of the second gene copy on the homologous chromosome).*

These issues are discussed in depth elsewhere; here it is sufficient to note that genetic context can result in up to a twentyfold change in induced mutation frequencies in autosomal genes (Bradley and others 1988; Amundson and Liber 1991). There is strong molecular evidence that in most circumstances, a DNA deletion mechanism dominates mutagenic response after ionizing radiation, and it is for this reason that the genetic context of the mutation is of great importance.

In illustration of this, radiation mutagenesis in cells hemizygous (one gene copy deleted) for autosomal APRT (adenine phosphoribosyltransferase) is constrained by the proximity of an essential sequence; induced mutation frequencies are relatively low, and only ~20% of induced mutations are of the deletion or rearrangement type—many deletions will have led to cell death.

By contrast, radiation mutagenesis at the X-linked HPRT gene is much less constrained by neighboring sequence; induced mutation frequencies are substantially higher, and ~70% of induced mutations show HPRT deletion or rearrangement—many more will have been tolerated. Stated simply, gene loss mutations are characteristic of radiation, but their recovery in viable cells can be a major limiting factor.

Also, gene amplification can result from the process of DSB repair (Difilippantonio and others 2002). As shown later, these features are important for consideration of carcinogenic mechanisms and are also discussed in respect of germline mutagenesis.

Deletion and rearrangement of APRT, HPRT, and other target genes do occur spontaneously but are generally less frequent than point mutation; in the case of most chemical mutagens, there is a strong bias toward the induction of point mutations…

Studies of the effect of radiation quality on the induction of gene mutations show a relationship similar between relative biological effectiveness (RBE) and LET to that noted for chromosome aberration induction. Mutagenic effectiveness peaks at a LET of 100–200 keV μm^{-1}*, with maximum RBE values usually in the range of 7–10 based largely on initial slopes of the dose-response.*

Molecular analyses broadly suggest that a DNA deletion mechanism predominates for all radiation qualities, but there are some conflicting data on this issue.

DNA sequence data for radiation-induced intragenic deletions in APRT and larger deletions encompassing HPRT indicate the frequent involvement of short direct or inverted DNA repeats at deletion breakpoints. The presence of these short repeats is highly suggestive of an important role for illegitimate recombination processes in mutagenesis and, as for chromosome aberration induction, the involvement of DNA DSBs and error-prone NHEJ repair.

Evidence for a close relationship between gene mutations and chromosome aberrations is that several induced gene mutations are associated with macroscopic region-specific chromosomal deletions or rearrangements.

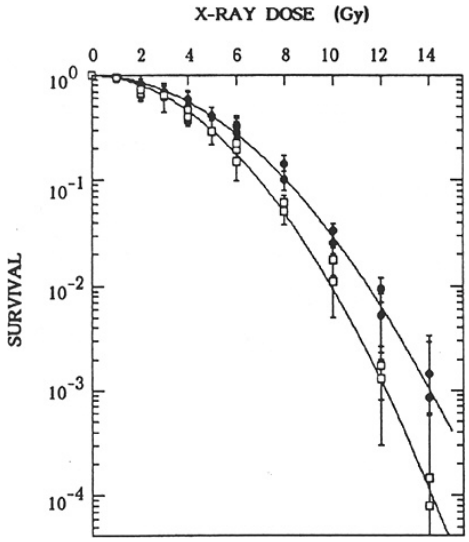


FIGURE 2-2 Effects of preirradiation on clonogenic survival of mouse m5S cells. Closed symbols represent results in cells in G_1 preirradiated with 20 mGy of X-rays 5 h before graded doses of acute radiation. Open symbols represent results in cells in G_1 given graded doses of acute radiation only.

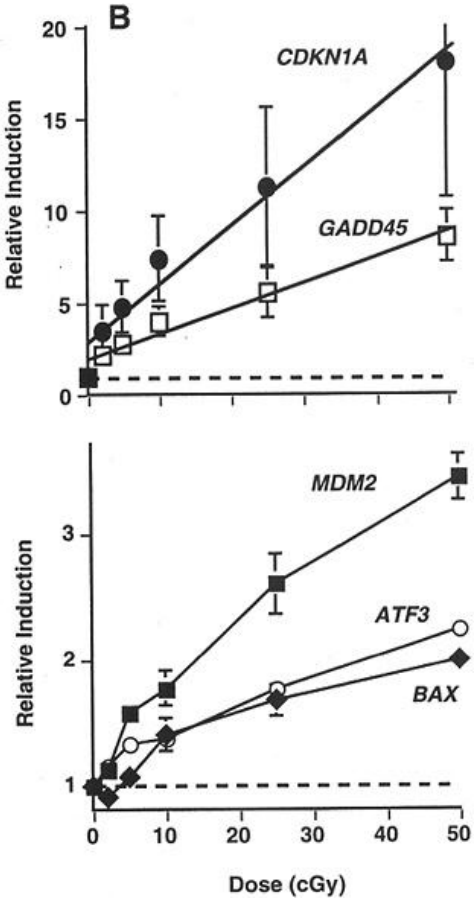


FIGURE 2-4 Maximal induction of CDKN1A (●), GADD45 (□), MDM2 (■), ATF3 (○), and BAX (◆) by low doses of γ-rays. Points are averages of four independent experiments; error bars are standard errors. Dashed line indicates basal level in untreated controls; solid lines were fitted by linear regression through the data.

The following Table is a modified version of what was in the NAS study and it looks at the dosage issues and certain impacts.

System (including exposure conditions and acute α[a] or LDR[b])	End Point	Dose Range, mGy	Curve Shape	Frequency of Events per Viable Cell per Milligray	Comments and References
Human fibroblasts in G_0	Immediate PCC fragments	109–6000 (acute)	Linear	6×10^{-3}	LNT[c] extrapolates to 5 mGy (Cornforth and Bedford 1983)
Human fibroblasts in G_0 α-component-metaphase	Chromosome dicentrics and rings	1000–12,000 (acute)	Upward curvature	5.8×10^{-5}	(Cornforth and Bedford 1987)
Immortal human lymphocytes in G_2	Chromatid gaps	50–500 (acute)	Linear	2.5×10^{-5}	LNT > ~50 mGy (Puck and others 1997)
Human lymphocytes in G_0 (six laboratories)	Chromosome dicentrics	3–300 (acute)	Linear	2.9×10^{-5}	LNT > ~20 mGy (Lloyd and others 1992)
Human primary fibroblasts in G_0 (acute α-component)	Chromosome aberrations	1000–6000 (acute)	Upward curvature	5.8×10^{-5}	α-Component for acute corresponds to linear dose-response for LDR (Cornforth and others 2002)
Human primary fibroblasts in G_0-0.5 or 1 mGy/min	Chromosome aberrations	300–6000 (LDR)	Linear	4.9×10^{-5}	LNT > 300 mGy (Cornforth and others 2002)
Mice—daily doses of 6.4, 18.5, or 55 mGy for 21, 42, or 63 d, respectively	Chromosome translocations	100–3500 (LDR)	Linear	1.2×10^{-5}	LNT > ~100 mGy DDREF[d] of 4–6 for 1–2 Gy acute exposure (Tucker and others 1998)
Nuclear workers at Sellafield—lymphocyte cultures	Chromosome translocations	50–1000 (LDR)	Linear	1.1×10^{-5}	LNT > 50 mGy (Tawn and others 2000a, 2004)
Cleanup workers at Chernobyl—lymphocyte cultures	Chromosome translocations	~95 (LDR)	?	1.9×10^{-5}	Increase of 30% (10–53% p < .002) relative to controls (Jones and others 2002)
Chinese hamster cells with human chromosome 11	Loss of antigen on chromosome 11	250–1500 (acute)	Linear	7×10^{-6}	LNT > ~ 250 mGy (Puck and Waldren 1987)
TK6 human lymphoblasts—daily doses of 10, 25, 50, or 100 mGy for 1 month	HPRT mutations	50–2000 (LDR)	Linear	6×10^{-9}	LNT > ~50 mGy (Grosovsky and Little 1985)
Mice—T lymphocytes in spleen—chronic at 0.69 mGy/min or 0.1 mGy/min	HPRT mutations	300–6000 (LDR)	Linear	3×10^{-9}	LNT > ~300 mGy DDREF of ~1.5 for acute <2 Gy (Lorenz and others 1994)
Cleanup workers at Chernobyl—lymphocyte cultures	HPRT mutations	~95 (LDR)	?	5×10^{-8}	Increase of 41% (19–66% p < .001) relative to controls (Jones and others 2002)
Chinese hamster cells with human chromosome 11	Genomic instability Translocations on chromosome 11	1000–10,000 (acute)	Linear	3×10^{-5}	Based on percent unstable clones with BrdU saturates at 30% (Limoli and others 1999)
Chinese hamster cells (CHO)	Genomic instability *de novo* HPRT mutations	2000	?	5×10^{-5}	Based on percent unstable clones; from 4 to 12 Gy saturates at 20% (Little 1998)
Melanocytes in irradiated mice	Genomic instability gene deletions	10–1000	Linear	8×10^{-5}	LNT > 10 mGy, but supralinear from 0 to 10 mGy (Schiestl and others 1994)

6.3 NAS STUDY NEEDS

The NAS study makes several recommendations. We critique them here.

Research Need 1: Determination of the level of various molecular markers of DNA damage as a function of low dose ionizing radiation. This is an issue we have been working on in this report. It is not only critical to understanding backscatter but the whole issue. The problem is the details of DNA damage. We have shown the energy levels. Yet we also have shown that we still need a better probabilistic model for collisions with x-ray photons.

Research Need 2: Determination of DNA repair fidelity, especially with regard to double and multiple strand breaks at low doses, and whether repair capacity is independent of dose. DNA repair is the process that as we go through mitosis we either stop the process and fix it or the cell dies off. In cancer this does not happen. We understand cell cycles somewhat but the knowledge still fall short.

Research Need 3: Evaluation of the relevance of adaptation, low-dose hypersensitivity, bystander effect, hormesis, and genomic instability for radiation carcinogenesis. This is a major problem that is somehow given short shrift.

Research Need 4: Identification of molecular mechanisms for postulated hormetic effects at low doses. This is a favorite of someone on the panel and frankly makes no sense.

The others are apple and motherhood issues worth stating but not commenting upon. They are:

Research Need 5: Tumorigenic mechanisms

Research Need 6: Genetic factors in radiation cancer risk

Research Need 7: Heritable genetic effects of radiation

Research Need 8: Future medical radiation studies

Research Need 9: Future occupational radiation studies

Research Need 10: Future environmental radiation studies

Research Need 11: Japanese atomic bomb survivor Studies

Research Need 12: Epidemiologic studies in general

7 CONCLUSIONS

As we have argued, there is significant concern for the nexus between backscatter x-rays and the potential for cancer. Our argument related to melanoma amongst a subset of people with an existing predisposition. Our argument was simply that there exists a small subset of people, Celtic in origin, who have dysplastic nevus syndrome, and thus when exposed to backscatter which penetrates to the melanocyte layer may induce additional genetic changes setting in motion a melanoma. The issue is that backscatter is lower dose but administered to frequent travellers often, and since the danger is most likely during mitotic change or possibly during transcription that it is the frequent low dose that may set off a problem.

We then argued that the TSA is in essence performing a substantial experiment that the FDA would never approve of. In fact we argue that since the x-ray is controlled by the FDA that before TSA can use this it must demonstrate no harm. But alas this is not the issue.

Rep King of New York, has stated that if one objects to this screening that they have "blood on their hands". Perhaps the good Congressman would think of those of us with such predispositions and their blood. One does not object to security that does not endanger the innocent, but the unchecked use of potentially harmful x-rays may endanger a small subset of humans who have done harm to no one.

According to The Hill:

Speaking on Fox News, the ranking Republican also sharply criticized talk of slowing the security system down in a Wednesday "Opt-Out Day," which never materialized.

"I think some of the hysteria that was generated, of people actually saying that they would try and slow the system down yesterday, well then, if you have a plane that had gone down the blood would have been on their hands," he said.

King said there would always be trial-and-error in the TSA evolving and trying to come up with the best systems, but "right now I think the body scanners are the best we think we have."

The problem is simple, use Bayesian statistics. That means profiling. On 12 September 2001 I took a flight from Prague to Paris. The Air France pilot went down the aisle and sent people packing he felt uncomfortable with. Extreme, but it was Bayesian at the time. In my flights on El Al the questions are always penetrating and to the point. Yet with TSA one seems to see that there is a collection of folks going through the routine who were selected on a lowest bidder contract. El Al gets the best, TSA gets the cheapest. What would one expect.

The NAS had written a report on backscatter which was long and in places tedious to the extreme. A more succinct paper is in a letter by a few physicians and scientists at UCSF which was sent to the White House and appears on its Web Site. Strange that this has not gotten much attention but seems to stay on the site.

The letter states in part:

The physics of these X-rays is very telling: the X-rays are Compton-Scattering off outer molecule bonding electrons and thus inelastic (likely breaking bonds).

Unlike other scanners, these new devices operate at relatively low beam energies (28keV). The majority of their energy is delivered to the skin and the underlying tissue. Thus, while the dose would be safe if it were distributed throughout the volume of the entire body, the dose to the skin may be dangerously high. The X-ray dose from these devices has often been compared in the media to the cosmic ray exposure inherent to airplane travel or that of a chest X-ray.

However, this comparison is very misleading: both the air travel cosmic ray exposure and chest Xrays have much higher X-ray energies and the health consequences are appropriately understood in terms of the whole body volume dose. In contrast, these new airport scanners are largely depositing their energy into the skin and immediately adjacent tissue, and since this is such a small fraction of body weight/vol, possibly by one to two orders of magnitude, the real dose to the skin is now high.

This is what we said a year ago. The comparison to flying in an aircraft is nonsense. X rays have unique photon frequencies matched to bond lengths of certain control elements of melanocytes.

They continue:

Our colleagues at UCSF, dermatologists and cancer experts, raise specific important concerns:

• A) The large population of older travelers, >65 years of age, is particularly at risk from the mutagenic effects of the X-rays based on the known biology of melanocyte aging.

Yes, that is what we said a year ago! Specifically demethylation of control pathways in melanocyte control.

Then they state:

Moreover, there are a number of 'red flags' related to the hardware itself. Because this device can scan a human in a few seconds, the X-ray beam is very intense. Any glitch in power at any point in the hardware (or more importantly in software) that stops the device could cause an intense radiation dose to a single spot on the skin.

This is the problem, the scanners are flying spot scanners using low power x rays which can accumulate and the systems seem prone to failure.

They conclude:
In summary we urge you to empower an impartial panel of experts to reevaluate the potential health issues we have raised before there are irrevocable long-term consequences to the health of our country. These negative effects may on balance far outweigh the potential benefit of increased detection of terrorists.

However if it is another NAS study it would be worthless. It must be an in vivo study where the pathways are studied as well!

Of course the FDA responded to assure the White House that there is no such problem[23]. This is the FDA folks, that means pure unmitigated politics.

The FDA states in its letter:
However, the concern that "the dose to the skin may be dangerously high" is not supported. The recommended limit for annual dose to the skin for the general public is 50,000 μSv9. The dose to the skin from one screening would be approximately 0.56 μSv10 when the effective dose for that same screening would be 0.25 μSv11. Therefore the dose to skin for the example screening is at least 89,000 times lower than the annual limit.

The data they rely upon is:

NCRP report no. 116 Limitation of exposure to ionizing radiation (1993), page 56

This 1993 report is two decades old and fails to deal with pathway damage, it was not known then! That is the issue. And that is the issue that FDA grossly neglects. The letter concludes:

In summary, the potential health risks from a full-body screening with a general-use x-ray security system are miniscule. Several groups of recognized experts have been assembled and have analyzed the radiation safety issues associated with this technology. These experts have published recommendations, commentaries, technical reports, and an American national radiation safety standard as a result of their analyses.

This is in my opinion the height of arrogance. What tests are done. I have been on these panels and staff, often Government controlled, write the report sections, and the battles over words can often be intense but are won by who controls the report. The UCSF people have a clear and well founded concern that is dealt with by the equivalent of a clinical study. That is supposed to be the FDA's duty but alas with the current administration there is no such professionalism in my opinion.

For example from the FDA's site[24]:

In 42 minutes of ordinary living, a person receives more radiation from naturally occurring sources than from screening with any general-use x-ray security system.

This is a simple example of the ignorance and arrogance in my opinion. They are comparing apples and oranges. Cosmic rays are not x rays and x rays of specific wavelengths and scattering in a Compton mode will cause specific bond breaks that start a process in certain people that may very well lead to cancer.

Thus having examined the available data, unlike the FDA and others, I believe that the data suggests the following:

1. The impact of Compton Backscatter is most intense on the top skin layers, 1 cm and less. The calculations used were assuming full body concentration of the radiation. In fact the radon, the same amount, is applied to only 0.001% of the body volume thus making it much more intense that full body radiation.

2. The major concern is that the melanocytes may be impacted upon by a bombardment of x-ray photons. The impact would most likely be on pathway elements which would most subject the individual to a melanoma.

3. There is a great deal of clinical ignorance at this stage and it is essential that before this deployment continues that a full and complete study be performed. Unless such is done there may be clear and present dangers regarding the continued use of this form of radiation.

4. The analyses done in pursuit of Government objectives have failed to adequately analyze the issues. They fail in that they do not look at the genetic issues and rely upon decades old studies, the Hiroshima studies, and try to extrapolate from them. There is a wealth of new data regarding pathways and these have not been examined in any way.

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