Nuclear Medicine

Lecture by William F. Bethard
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Transcribed by: Sherry Yin

Time	Transcription
00:00	Dr. William F. Bethard: I think perhaps I'd better start, although this is not this type of a program like the magician who asks for a volunteer. I'd like to have one person volunteer to write something on that blackboard for me while I'm talking. Shall I appoint a volunteer? You come right here. Yeah, anyone. Would you copy this, not this, would you just copy that on the blackboard there for me?
00:30	Speaker 1: I will try.
00:31	Dr. Bethard: All right, fine. While he's trying, while we'll go on. I appreciate these opportunities to speak on the topic of nuclear medicine partly because I like to have a chance to, to express what I think are some errors in the, not only the nomenclature but perhaps in the content. I like to point out that nuclear medicine is really a bad term. It's one which has become popularized and one which even doctors who are engaged in the field use but it really is a misnomer because nuclear refers to any type of chemical reaction which is depend upon the properties of the, the molecular properties of the reactants. The molecular properties as opposed or as contrasted to the colligative properties and therefore, any type of biochemical reaction would be a nuclear reaction. But that isn't what we mean when we say nuclear medicine. We mean the type of medicine which has been studied and studied by means of the radioactive nuclei, radioactive isotope, so I would like to correct the title and, and submit the title of the use of radioisotopes in medicine if you will.
02:02	Dr. Bethard: As I mentioned, doctors are particularly bad in this respect because not too long ago there was a Society of Nuclear Medicine formed and to show you how, how obtuse I can be, I joined the thing even though I don't agree with the name. I also like to point out that I speak with a little diffidence to a high school audience. One should, one almost assumes it will be easy but certainly, it is not. I went to a high school open house a few weeks ago and attended some of the classes in math and physics and I decided I wouldn't try to touch those subjects in front of you. And then I went to a class in speech arts and I decided maybe I better not try that either. So, I hope that you will go along with me and in a rather amateurish type of performance. As you will see in the yellow sheets which have been passed out, I will touch first on the historical aspects of the use of radioisotopes and to me, this is a very interesting background. It gives one a little perspective as to why we do as we do do, you might say.
03:23	Dr. Bethard: And we go back, well this is thought to be a relatively new thing but really it isn't that new. This started before the turn of the century, It started in 1895 when Doctor Röntgen, or Mr. Röntgen, discovered that there was a mysterious type of ray which had a peculiar effect on photographic film and he, since he did not know any of its properties and did not know where it came from he called it an

X-ray. And oddly enough a year later the fact that these rays could be produced by natural substances was discovered by Becquerel. And two years later the Curies, about two years later after much work, isolated radium from tons of pitchblende which I'm, a story I'm sure you're familiar with. And then by 1900, five years after the whole thing began, it became obvious that these peculiar rays, these x-rays or as we later found gamma rays, from natural sources had a differential effect on, on tissues. And certainly, people and the doctors knew about cancer then, cancer is an old disease it was described 400 BC, and everybody since that time has been looking for a cure but as you know we have not yet found it. But in those days it looked quite promising because within a period of five years, a new ray was discovered which had a lethal effect on cancer tissue but which would not kill normal tissue and things looked very good but unfortunately, the progress did not continue at that rate.

05:17 Dr. Bethard: And I've often thought that although we consider these days as being progressive and being advancing, if any of those early workers came back, if they could come back and come to life again and see what we were doing, they really would be very disappointed. After the wonderful start they gave us, we still can't cure cancer. And in the field of radiation, although thousands and thousands of articles have been published, we really don't know very much more about why radiation kills the cell than they did sixty years ago. Between 1900 and 1930, there arose a new specialty in medicine called radiology and at that time the radiologists were concerned particularly improving the dosimetry. That means in determining how much radiation they were giving or how much radiation a person was getting. And they had a real vested interest in this because they were using their own hands to measure the doses and it wasn't until later they began to realize that this was not good. That the effect of radiation was cumulative and that they could take a picture of their hand and set the two but that setting - so they got a good picture and then take a picture of the patient - but every time they took a picture of their hand it added a little bit more damage to the tissue which was already damaged, which already been done to the tissue.

06:50 Dr. Bethard: And soon, well not too long thereafter, some of them began to lose their fingers and some of them developed cancer in the skin of their hands. So that they had a real purpose in wanting to know, wanting another way of determining how much dose they were giving. They also started to develop new types of technical things such as shock-proof apparatus and so forth. So it was a hiatus of at least 30 years before any more biological work was done, of really any note. And then there was another impetus to do this work. In 1934, Doctors [Frédéric and Irène] Joliot and Curie in France - this is not the original doctor [Marie] Curie, this was her daughter - they discovered that radioactivity could be induced artificially. So I think they used sodium. They put sodium in a flux of neutrons while the sodium would become radioactive. And as we know it now, it was Sodium-24. And that was another great big step because then people could begin to see that if

they could pick the right chemical and make that chemical radioactive, then it would, might be possible to make that chemical go right to a tumor and deliver its radiation to the tumor. It was also a very astounding discovery from the field of physics but I'm speaking from the standpoint of the medical field.

08:28 Dr. Bethard: So it became at least theoretically possible to pick a what is called or what is referred to in other fields a Magic Bullet if you ever recall Ehrlich his trials with 606. Well, that was done shortly thereafter. About two years later, in 1936 Dr. John Lawrence, Dr. John H. Lawrence, and his colleagues began to think about various types of elements which would go to tumors. And they reasoned like this, they said well, the most common substance in a tumor, the most important substance is a nucleoprotein. That's the substance of which the tumor is made. So of all the elements in the nucleoprotein, they picked phosphorus. And they reasoned that where the nucleoprotein was being turned over or being made and destroyed most rapidly, that would be where most of the phosphorus went. And they tried that in, in animals. They gave tumors to rats and mice, certainly, sure enough, that's what happened. Most of the radioactive phosphorus went to the tumor and there was a decided radiation effect. Well that was, it was very good rationale and I think it's a tribute to those workers that even today we don't have a radioactive isotope which is much better in this respect than P-32, with which they started.

10:01 Dr. Bethard: There was some drawback at that time because we didn't have any reactors and the production of P-32 was rather laborious and very expensive. And I think perhaps it was little more than fortuitous that Dr. Lawrence's brother, Dr. Ernest Lawrence, was the man who invented the cyclotron and he had the only cyclotron in the world so that was the only place that the P-32 could be made. And thank you very kindly.

10:30 Speaker 1: I hope it’s right. I don’t know.

10:32 Dr. Bethard: It’s close enough. At any rate, he had the vision and the energy, and the facilities all in the same time and the same place and he did a what I think was a great piece of work. About six or eight months ago, it was my privilege to have dinner with Dr. Lawrence in Berkeley. He and another man named Dr. [Paul] Aebersold had been working together on this. Dr. Aebersold at that time was a student at Caltech and they took me to lunch at a little place called Trader Vic's in Berkeley and we went back to the table where they used to sit every evening and discuss their work. And I didn't say a word for the whole meal but it was fun to sit there and listen to them reminisce about the problems they had in, in making P and using P-32. [Bell rings] The next great impetus they had would came and in the use of radioisotopes in medicine was the advent of large reactors. For this, we have World War II to thank. This is one of the good things, one of the few good things that came out of World War II.

11:43 Dr. Bethard: The reactors, well this came out of the Manhattan Project, The bomb was being made, it became obvious that a chain reaction could be controlled and so reactors were made and that gave us a good inexpensive source of neutrons with which to make P-32. And ten, twelve years ago when I used to give P-32 to patients to good deal, why we have a little cup or a little syringe and the charge for that would be about anywhere between 25 and 35 dollars and every once in a while one of them is going to complain about the price. Well, it's still not inexpensive but then I pointed it out to him that the same amount of P-32 ten years prior to that would cost about 10,000 dollars. And that, after that there were not very many complaints. It has been tried in, in various diseases and we'll go into that in a little bit. I would like to go on now, so much for the history, going on now to some of the uses of radioisotopes. And I'd like to point out that we have to define a couple of terms. Not only is it necessary for me to define them to you but it also has been necessary for the doctors to learn them because not very much of this is taught in medical school or at least was taught.

13:11 Dr. Bethard: It's beginning to be taught more and more and doctors who have, who hurried through the pre-medical work, took the short courses, and so forth, are finding themselves a little bit of a disadvantage because of the physics and chemistry which are entering into the medical sciences. First thing I'd like to define is a millicurie, is because on the slides which come in a little bit while you will hear me refer to millicuries and microcuries, and I think you ought to know what they are. Well, it is all based on the radioactive emanations which come from radium. And in deference to the Curies, the units are called curies. So that the amount of radioactivity which comes from one gram of radium is called one curie. And the amount of radioactivity which comes from one milligram of radium is called one millicurie or one-thousandths and the amount of radioactivity which comes from one-millionths of a gram or one microgram is called a microcurie.

14:25 Dr. Bethard: Another term which I think it would be useful to define would be half-life. This is a very, it has a very specific denotation in mathematics. It is applicable to physiological systems and it's become quite a popular term. As it's become popular you'll find it's being misused more and more but it does have a definite place in the use of radioisotopes again which we'll see in a moment. The half-life is that amount of time which is required for one-half the radioactivity of any radioactive sample to disappear. And as I mentioned it, it has certain mathematical implications in that from that piece of data or that datum why the turnover rate, the turnover maths can be calculated. Another set of definitions which I just touch on, I don't think I'll go into in any detail, are the way doses, doses in tissues are described. There are, this is the sort of a state of confusion started out with roentgens. Roentgens are applicable really only to the energies which come from gamma rays which come from radium so that then rep or roentgens equivalent physical is substituted, that didn't work out too well. And now the most popular type of unit is the rad. The rad is the amount of gamma radiation which will provide

one hundred ergs of energy per gram of tissue. I don't think we need to go into that any further. Although if some of you read that in the, in your books or literature while you'll have you will have a memory of having heard it before anyhow.

16:24 Dr. Bethard: The uses of radioisotopes fall into two general categories and the first of these is therapeutic or therapy treatment. The second of these is a tracer application or experimental applications and I like, I would like to go through some of these and give an example of each. The first category, the therapy, is the one that has received the most publicity. I think that's a little bit too bad because I think it's going to turn out to be the least important, but again it stems from the fact that for a while it was thought we had a cure for cancer. We could direct radiation toward any tissue, destroy the tissue, and leave the normal tissue present. The newspapers were partially to blame for the popularization of this and the promise that everybody feels is coming because of the therapeutic, therapeutic aspects of radioisotopes. But in reality, I think we are gonna learn a lot more, we'll be, the real dividends will be from the tracer applications. From the therapeutic point of view, we've already mentioned P-32. It's turned out it's been used in many, many diseases. It's turned out that it's excellent treatment for some of the blood disorders such as leukemia. Another disorder which I will tell you about in a moment called polycythemia, too much blood so to speak. It is good for certain tumors, tumors of the breast, and so forth, which will go to bone because P-32 goes to bone and thereby delivers some radiation in the vicinity of the tumor.

18:16 Dr. Bethard: P-32 is at present obtained from Oak Ridge [National Laboratory]. One has to have a license from the Atomic Energy Commission to get it. One has the license. One orders it from Oak Ridge. It's shipped in a liquid form. It's usually pre-standardized but not always and one of the requirements for getting the license is that you have to have enough equipment to be able to count it and you have to have a standard for comparison so you know how much P-32 you're giving. [Bell rings]. When you have all that when you have supplied evidence that you have used it under someone else's supervision and learned how, then it's quite all right for you to go ahead and give it. And it's still being used in large quantities throughout the United States for those, for the blood diseases that I have mentioned. When it's given, it goes almost directly and almost instantaneously from the blood to the bone marrow. It doesn't, that's not the only place it goes but that's the place it goes most rapidly and to the greatest extent. The second place oddly enough is in the lining of the intestinal tract. It doesn't have, it hasn't turned out to be of any value, say in cancer of the stomach, oddly enough but it does go to those tissues.

19:40 Dr. Bethard: The second radioisotope which is of great value is radioactive iodine. This is of value not only in treatment but also in tracer studies and it, as far as quantity goes, is probably used more than any other radioisotopes at the present time. And it's used for, well it's used by virtue of the fact that it's taken up almost

completely by thyroid tissue. So if one has a cancer of the thyroid, why one can give large amounts of radioactive iodine. It will go to the cancer, in most cases not all, depending to some extent upon the activity of the tumor in producing thyroid hormone. But in many cases, it will go and one can get good therapeutic effects. I can remember a patient we had at the University who had a cancer of the thyroid where they spread or metastasis to the brain and he was having all sorts of neurological symptoms, including loss of eyesight and so forth. And he was treated with radioactive iodine and as far as I know, this was some years ago, he is still in good condition and his neurological symptoms disappeared. So it does work on occasion but it's certainly no panacea.

21:02 Dr. Bethard: Iodine-131 also has tracer applications which we will get to in a moment. There are some other radioisotopes which have been investigated and which are used from time to time but not regularly and one of these we will see on a slide is Arsenic-76. Arsenic is a radioisotope which has been used, well Arsenic itself has been used in leukemia for a long time but the radioactive form was used about ten years ago. It happened to be started at the place where I was working. It has a short half-life of about 24 hours and has to be made very close by. So instead of getting it from Oak Ridge, we sent it out to Argonne National Laboratory, had it made, and was brought in the hospital and we gave it right away. It worked fine till all of a sudden one day the truck upset and we had radioactivity all over the south side of Chicago and we decided we better be more careful. So we didn't use much of it anymore. It didn't do any damage but the people didn't like it very well.

22:08 [Audience Laughter]

22:11 Dr. Bethard: Other isotopes such as gallium has been, it's another short-lived radioactive isotope which goes to bone. It's been tried in bone tumors. It works fairly well but no better than P-32 or no better than radiation and so it was given up. Gold-198 has been used and it still is on occasion. We'll see a slide about that very shortly. So much for the therapeutic aspects. I would like to touch a little bit on the tracer applications because as I just said a moment ago I think that's where the future lies. But in using these as tracers one has to assume that there is no what we call isotope effect. In other words, carbon-14 is metabolized in the body the very same way as carbon-12 or carbon-13. Usually, that's a pretty safe assumption. I think that it's very true for iron-59 as composed of iron-56 or 57. But it's not always true and one always has to keep that in the back of the mind, of his mind and I'll tell you why. There is, well as most of you know there are two heavy forms of hydrogen. There is hydrogen-2 or deuterium and hydrogen-3 or tritium. And if one substitutes in the diet of a small animal such as a mouse or rat, deuterium or hydrogen-2 instead of hydrogen-1, the animal will die.

23:48 Dr. Bethard: And it will live up until until you get about 30 percent of the water in the diet composed of deuterium oxide, and then it dies. So, something in the

animal can distinguish between hydrogen-2 and hydrogen-1 and it's a lethal effect. So as the radioisotope in use becomes lighter and lighter, then one has to become more and more suspicious of an isotope effect. I think, however, it's fair to say that most all of the work which has been published is quite safe in this respect because most of it is with the heavier elements. One must also be sure that the element itself is not toxic to the system you are studying because if you have to get so much of it that you change the system then you don't get the proper results. In general, there are three categories of, of studies which are done in tracer work. And perhaps the most important is the study of kinetics and the study of rates, and rate constants, and I'm sure those of you in mathematics will realize that this can be somewhat complicated, and not only would I rather not go into it at the present time but I'm not sure I could. Another, just to say however that this is a measure of how fast the processes are going on within the body. I will have some slides to demonstrate that and show you why it's important in a moment.

25:27 Dr. Bethard: One example for this is iron-59 and that's the slide I have. Another example would be iodine-131 because and this is a very common clinical tool, it's one that we use every day to try to diagnose certain diseases of the thyroid. If one knows how fast the radioactive iodine goes into the thyroid or how fast it comes out then one can get some ideas to how active the thyroid gland is and whether or not this activity is within normal range. If it's too active, then we assume the patient has hyperthyroidism. If it's not active enough, then we assume that they have hypothyroidism. It's particularly important in little babies when they can't tell you their symptoms. You don't know how they're feeling and so this is about all it one has to go, to go by. The second way in which radioisotopes can be used as tracers are in distribution studies. If one wants to know, for example, where or how a toxic something like plutonium is or polonium or uranium, any of the metals which we have to deal with in the, around the Atomic Energy Commission facilities.

26:49 Dr. Bethard: Well one takes a little of the radioactive forms, or takes the form, which is an alpha, most of them are alpha-emitters, injects it into the animals, sacrifices the animals, and then takes bits of tissue and tells where these things go. So that if it ever happens to a human being, as it has in the past by accident, we'll know just where to look for diseases to develop or we'll know just where to look to make diagnoses. So they can be used to study distribution of chemicals. And the third important way is by isotope dilution. Now that's a fancy way of saying the measure of, referring to measurements of volume. And as an analogy, I can point out that if one has a receptacle of water, it's inconvenient to measure it in CCs [cubic centimeters] by putting it into a graduate, a graduated cylinder. If one say dropped a drop of ink into the bottle and then one compared the blackness of the ink before it was dropped in and the blackness of ink after it was dropped in, then one could tell how big a volume that the ink was dropped into. Well, we do that by using radioactivity. We know how much radioactivity there is, to begin with. We know how much there is at the end. Therefore, we know how much dilution

there is. Again I have a slide that more or less, experimental slide which will, will show that in a moment. I think before we go on to that, that thing, we might look at some of these slides.

28:32 Dr. Bethard: This is merely an example as to, of the slide to define a radioisotope, you might say. It's fairly self-explanatory. Notice on the left carbon-10 contains six protons and four neutrons. It's a radioactive isotope. Carbon-11 was probably the first radioactive form of carbon which was used in human experimentation. It has six protons and five neutrons; it has a half-life of about 21 minutes. It was first used by Dr. [Albert Baird] Hastings, who's now living in La Jolla. He did the work at Boston, at Harvard [University]. The isotope, the radioisotope was made at the MIT [Massachusetts Institute of Technology] Reactor and to do everything he wanted to do and to hear him tell about what he had to do, it was quite comical because within 21 minutes or at least 42 minutes of time, he had to do all sorts of chemical separations. Carbon-12 occurs in nature. It's not radioactive. There are six protons, six neutrons. Carbon-13 six and seven occurs in nature and then carbon-14 which I'm sure you've all heard about, it's the most commonly used radioactive isotope of carbon. It has six protons and eight neutrons. It has a half-life of some 5,100 years.

30:01 Dr. Bethard: Why one form should have a half, life of 21 minutes and the other 5,100 years, I have no idea and I don't think the physicists have any idea but it's a fact. Because of the long half, life of carbon-14, there was a lot of difficulty in getting the AEC's, or Atomic Energy Commission's, permission to use it in human, in human beings, in people. And rightfully so because one did not want to increase the amount of radioactivity to which a person was exposed. But about five, six or seven years ago, it was found that when carbon-14 was given to a person about 90 percent of it came out within the first 24-48 hours so that really presented no radiation hazard and since that time we've learned a great deal about human physiology and human biochemistry by the use of this one radioactive isotope. Next slide, please. This is merely an example of how, or of the nuclear reactions by which these radioisotopes are made. Let's forget the top line, take the second line right here. This is one way to make P-32. In that way the one starts with stable phosphorus or P-31, having fifteen protons and sixteen neutrons.

31:29 Dr. Bethard: One then subjects that to a neutron bombardment. The atom absorbs a neutron becomes unstable, becomes radioactive, and then is degraded to sulfur-32 by the emission of a beta particle. That was the way the first P-32 was made but it wasn't a very good way because the yield was not very high. Not much of the final mixture was P-32, much of it was P-31 and there was no good way of separating the P-32 from the P-31 so one had to use a lot of phosphorus to get a very little radioactivity. Now, let's go down to the bottom line. That's the way it's made at the present time. One starts with sulfur-32, sulfur target. It is then subjected to a neutron flux, the sum of the atoms of sulfur absorb a neutron and

become P-32 which is the, then emits beta particles and decays. But this way, you want to get a very high yield of P-32 because by chemical separation one can separate the remaining sulfur from the produced P-32 so that, when one when orders P-32 from Oak Ridge at the present time, one gets what they call Carrier Free. Means that every atom in the solution is radioactive and it happens only by virtue of the fact that sulfur-32 and P-32 are separable on the chemical grounds. Next slide, please.

33:17 Dr. Bethard: This is a slide that was made by the Atomic Energy Commission several years ago. I just like call your attention to this line. There are about 740 radioactive isotopes known. Of that 740, not more than a dozen are utilizable in any routine way in medicine or physiology. It isn't because it hasn't they haven't been tried, it's just because there's been no good uses found at least in the present time. Part of the problem is that many of the radioisotopes have such short half-lives that they can't be made in Oak Ridge and worked on out here. For example, oxygen-15 has a half-life of three or four seconds and it sort of limits the activity, limits the procedures. Just recently I've been working with an isotope or radioisotope, magnesium has a nine and a half minute half-life. We make it in the reactor at General Atomic and we use it in the laboratory about 200 yards away and we carry it back and forth in little motor scooters called the Blue Goose. Well, since the half-life was so short, we had to run pretty fast and we were all, we were called out by the safety officer for driving too fast and now they have governors on them all. [Audience laughter]. Next slide, please.

34:55 Dr. Bethard: This is a pictorial way of describing, describing decay curve. The ordinate up and down axis is the amount of activity and the abscissa or the horizontal axis is the time. It happens at this time, this time axis is in hours. It's a hypothetical type, well it's really radioiodine because half-life is about, well I beg your pardon, it's not radioactive-iodine either. Half-Life is about three hours. I don't know what isotope that is. The half-life of radioactive iodine is eight days and I saw that eight and thought it was iodine. But it's the same shape of curve no matter what the time axis is so that if you had radioactive carbon or carbon-14, then the time axis would probably be in thousands of years. But the important part is if one, this is a logarithmic or exponential function. So if one plots the logarithm of the activity on the ordinate, then this becomes a straight line. And from that one can do a number of maneuvers in graphic analysis, which I will particularly go into here. Next slide, please.

36:10 Dr. Bethard: This is the way we used to think, I say used to, it's not entirely true anymore. The way we used to thinking trying to determine whether or not a radioisotope would be valuable in medicine. First of all, it still has to be non-toxic. It should be free from impurities. It should not be localized to any great extent in normal tissues. It should localize in the tumor's tissues which one wants to treat. The half-life no longer has to be between one and fourteen days. This slide was

made prior to the time that carbon-14 could be used and it's nice to have, to be able to make it cheaply although that again is not prerequisite entirely. Next slide, please. This is a picture of the reactor at Oak Ridge. This is where most of the isotopes, radioisotopes used in medicine have been made. You probably have all seen pictures of them before so I won't go into it except to say that these are the uranium fuel elements running back and forth to control rods run up and down. The whole thing is in a large graphite moderating block. Around the outside is a tremendous casing of high-density concrete to protect, protect the workers from gamma radiation. They have, I've seen this one in Oak Ridge. I've seen a similar one in Brookhaven [National Laboratory] and it's really quite impressive.

37:41 Dr. Bethard: Next slide, please. Can't see this too well but this is a mock-up of the reactor which we used at General Atomic. This is a little toy compared to the other one but it's certainly a very handy thing. We can get quite high fluxes and it's a real convenient, really convenient gadget for medical work. The fuel elements are down here, some 53 fuel elements. Around the outside, there's a specimen rack. We can put all sorts of chemicals in here, we can put tissues in here. We can use it for subjecting most, most any sort of thing to neutron radiation. Around the fuel, elements is a graphite block and the whole thing is in water and anyone can see it so that you can see what's going on. The water is to protect us from the gamma radiation. Next slide, please. This is a view looking down. There is sixteen feet of water on top of it. As you look down you can see the holes for the fuel elements, these control rods going down here and this is the thing that goes down to the specimen rack.

38:50 Dr. Bethard: The only defect in the whole thing is it's hard to put live animals down there. You have to have some way of keeping them from drowning. At the present, well this morning as a matter of fact, some people from here, from Brookhaven, Brookhaven National Laboratory. And they were radiating mice and in a large model of this reactor and all we did was just to drive a, or to put, an aluminum tube about that big round down the bottom, make a watertight seal, we can put the mice down right outside the reactor. So even that can be overcome. I suppose you can use fish if you got into trouble. [Audience laughter]. Next slide, please. This is a diagram of how P-32 is, is utilized medically. It has here, the patient drinks the solution. It used to be that I gave it all by hypodermic and gave it all into the vein. Now I think probably this is right. It's better to drink it. We know a little bit more about the percentage which is absorbed so we can allow for that.

39:34 Dr. Bethard: Following that it goes to the bone marrow, some it goes to the gastrointestinal tract and it has the advantages of some selection as far as radiation goes and the, the radiation effect is prolonged. Next slide, please. The same sort of diagram with radioactive iodine. One can give it by mouth, doesn't, don't have to give it by needle at all. It all goes to the thyroid gland if there's a thyroid tumor and if it is manufacturing thyroid hormone for example, as here one

can find it by the radiation which is given off from the taken up radioactive iodine. Used to be a surgeon at University of Chicago who had done much of the original work in this respect and he had a mannequin which he carried around. You know one of these department store dummies and he would hide little specimens of radioactive iodine in them and take the mannequin to the various medical society meetings and you'd have the men in practice go along with the counter and find the metastases. It was rather impressive in this rather naive type of way. Next. [Audience laughter]

41:24 Dr. Bethard: This is one use I haven't mentioned up to now for radioiodine. Ordinarily radioactive iodine goes entirely to the thyroid, not entirely but 99 percent of it goes to the thyroid gland. So some of it comes out in the kidneys but 99 percent of that which is retained goes to the thyroid gland. There are ways of changing this and one way is to attach the iodine onto a larger molecule of, in this case, fluorescein so there's diiodine fluorescein but fluorescein does not go to the thyroid gland. Fluorescein goes, with some differential effect, to tumors and this has been used as a means of diagnosing brain tumors. As shown here, a brain tumor will take up more of the radioiodinated fluorescein than normal brains. So that by counting over the top of the skull one can get some idea as to whether or not there is a tumor present and if there is, how extensive it is. It's not foolproof, it's not used routinely but it's, it's being experimented with not only in the form of fluorescein but other types of radioisotopes are being used in the same way. Next slide, please. This is the way that it has been devised for giving radioactive gold. Radioactive gold as a short-lived radioisotope lives a half-life of about between 24 and 48 hours.

43:01 Dr. Bethard: It can be flown by jet from Oak Ridge and it can arrive with a reasonable amount of radioactivity left. It is not used necessarily for leukemia by giving by mouth and so forth, but it comes in very handy when a person has a cancer of the, some organ in the abdomen which is spread to the point where surgery cannot be done and yet which causes a lot of fluid to form. Fluid is very uncomfortable. It's very debilitating and one can cut down on the formation, one can really help the patient. So that's the way it's used now. The, say either in the abdomen or the chest, the fluid is drained out, a large amount, 100 and 150 millicuries of radioactive gold are put in, the radioactive gold. It's a colloidal form. It coats the lining of the cavity and gets onto the tumor and kills part of the tumor. I think it's fair to say nobody has ever been cured this way but a lot of people have been made to feel better, hence it's worthwhile. Next slide, please.

44:16 Dr. Bethard: This is a slide of blood count, of a blood count on a patient who I used to take care of who had chronic leukemia. These bars on the lower line represent the amount of P-32 that was given. For example, he got three millicuries here and the frequency of the bars represents the number of times it was administered. As you can see, as he was getting P-32 the white blood count, this represents not

only white blood count, but another type of cell called platelets, which moved together came down to a reasonable level. Actually, was about thirty, thirty, forty thousand here, came down to within normal range. At the same time, the red blood count came up and that was, that means he had a good response and it was well worth doing. The spleen was very large when I first saw him as it is frequently leukemia and it went down so it was no longer what we called palpable. It could no longer be detected by feeling. Next slide, please.

45:22 Dr. Bethard: This is the same sort of thing only with a different disease called polycythemia. This is a disease in which the bone marrow is no longer controlled by the usual homeostatic mechanisms and it sort of races and makes too much blood so we have to give something to slow it down. This patient had something which you, actually the patient was bled. Some of the blood was taken off and then the radioactive phosphorus was given and as you can see the blood ran along on a level course for a long time, over a year and then the effect wore off and the blood went on up. That's the usual course of events. The radioactive phosphorus can be given once and usually that lasts for a year and it's very good treatment. It still is probably the best treatment for polycythemia even though P-32 was the first radioisotope investigated. Next. This is a blood count, a white blood count of a patient who has leukemia who had leukemia. I say had because it's about ten years ago and I lost track of him. I don’t know where he is now and he was treated with arsenic-76. This was the time when we were rushing him into Argonne laboratories and his white count was up above 150,000, as you may know, or may not know though the normal value was below 10,000 and he was given a large amount of arsenic-76. His count came right down normal and I think you can say we helped him. I hope so. Next slide, please.

46:59 Dr. Bethard: This is another example of some of the other radioisotopes which can be used medically. Strontium-90 all of you’ve heard a lot about it from the point of view of fallout and content of the body and so forth. It has a medical effect, in that it can be used in places where one does not, where one wants only surface or superficial radiation. Strontium-90 emits purely beta particles or electrons. It has no gamma radiation and in particularly in the eye where gamma radiation is harmful to the retina and yet one may have a tumor on the surface of the eye. Strontium-90 works very well because the beta particles don’t go any deeper than a half a millimeter in the tissue, so they don't reach the retina and yet you can get large amounts of radiation delivered to the surface. Next slide, please.

48:00 Dr. Bethard: This is a, one way of doing experiments with carbon-14. I show that this is an old, older slide and they're doing it with mice. They give the mouse some sugar and which radiocarbon has been built in and then they measure the amount of carbon, radioactive carbon dioxide which is given off. I show this because since then these studies have been extended to human beings and you put people in a thing like that and give them various types of sugars and measure the amount of

carbon dioxide given off. It's gotten to be quite a sophisticated type of experiment, in that some people with certain types of tumor will metabolize carbon, radiocarbon one way and another type of tumor will metabolize in another way or normal people will metabolize in another way. And this is, this sort of, these sort of data have been arranged so they will be printed on cards and one gets all sorts of information about the tumor in the person as he is sitting in that cell. Next slide, please.

49:14 Dr. Bethard: This is an example of a tracer application of radioactive iron. Now don't pay any attention to this, this part of the graph, just this part. If one injects into a person's arm a very, very small dose of, an entirely harmless dose, of radioactive iron, then measures the rate at which the radioactive iron leaves the blood, leaves the circulation, and plots it on a graph, one gets a line such as this. And normally half of it goes away in between one and two hours. The halftime here is a good deal shorter because this person was quite deficient in iron and this was an elderly lady who was anemic and we could show by this type of maneuver that she was lacking in iron and she was given iron and then things were all right, so-called plasma iron clearance curve. It's to me perhaps one of the best examples of tracer techniques as applied to clinical everyday medicine. Next slide, please. This is a corollary study to that and what we do here is to measure the amount of radioactive iron which then reappears in the blood, in the red blood cells because the only way the radioactive iron can get into the red blood cells is to go through the bone marrow.

50:45 Dr. Bethard: So if no red blood cells are being made, as is sometimes the case, then no radioactive iron or very little will reappear in the, in the blood. But if a lot of red blood cells are being made then a lot of the radioactive iron would be, would appear in the blood. And in this case, a lot of the radioactive iron appeared, almost 100 percent of the amount given appeared which again meant that she was lacking iron and we could tell it by this way and treat her accordingly. Now we have one more slide, this is a little bit more far-fetched you might say. Well, let’s have it now. This is an example of some of the confusion we go through in our animals in the laboratory. This is an experiment another doctor and I did several years ago. We were trying to determine by isotope dilution how much iron was in a rat and we took a lot of rats and injected some radioactive iron and then we plotted what we call a specific activity.

51:52 Dr. Bethard: Now specific activity is very simple. It’s merely the ratio of the radioactive iron to the all iron present. And we found that, after several days, why this specific activity, or the ratio of radioactive iron to regular iron, approached the common value in all tissues. That meant that if we could wait long enough we could inject some radioactive iron into the rat, wait several days and take a sample of blood and determine how much total iron there was and how much radioactive iron and then we could calculate the total amount of iron in the whole rat, not just

in the blood. And that we did and so far we haven't done it to people yet but it certainly would be possible to do it with people too. For those of you who are interested, there are 9.3 milligrams of iron in a normal rat. I think that's all the slides, is it not? Let's, I want to use, this is my last example here. This is a, to me a very, very interesting part of medicine. I don't think any of you are old enough to remember how serious a disease pernicious anemia used to be. But I can remember when I was a kid that one of my family's very, very good friends died and I found out later he died of pernicious anemia.

53:24 Dr. Bethard: About six months later, it was found that liver was good for pernicious anemia and since that time I think it's fair to say nobody dies of the disease anymore. Well, over a period of about twenty years, 22 years, from 1926 to 1948, it was tried, attempts were made to try to find out what there was in liver to keep people from dying of pernicious anemia, and many, many things were suggested and were eventually shown not to be the substance. But in 1948, there was presented a paper in Atlantic City, and I happened to be there at that time, in which this compound was described and that's vitamin B12 and this is the formula which the young man so kindly drew for us, which is thought to be, thought to represent vitamin B12. It's not accurate yet but I like to point out that as large a molecule as it is, there is a central atom of cobalt. That's right here. By making that atom radioactive, by using, by growing animals in solutions of cobalt-60, one can by animal bacteria, one can recover radioactive vitamin B12.

55:02 Dr. Bethard: It has provided, provided us with samples which we can do all sorts of experiments with and so much has been learned about vitamin B12 which we would never know any other way. And it has turned out that one microgram of this compound per day, one-millionth of a gram or one 500 millionths of a pound approximately, makes a difference between whether you live or die and that got me curious one time. I, using this formula, I figured out the molecular weight. It's not accurate perhaps, but if one calculates from Avogadro's number the molecular, the number of molecules in one microgram, one finds that there are 5 times 10 to the 14th molecules in one microgram of vitamin B12. Well, this was all prompted by the fact that I came across a datum which said there were 10 to the 15th cells in the human body. So theoretically, each cell needs one molecule of vitamin B12 per day. And I, I give this just as an example of the precision which we can reach and of the advantages we can have using radioisotopes as tracers rather than therapy.

56:53 [Audience clapping]

57:15 Speaker 2: [Unclear]

57:28 Dr. Bethard: Its disintegrations per second. Turns out to be 37 million disintegrations per second.

57:38 Speaker 3: [Unclear]

57:52 Dr. Bethard: That's the average remission as we say, the average time that the treatment lasts, a year. We usually give about 6 millicuries of P-32 and it costs about 5 dollars a millicurie, so it would be about 30 dollars.

58:14 Speaker 4: What does the body use vitamin B12 for?

58:19 Dr. Bethard: The question was what does the body use vitamin B12 for? Well, in the production of nucleoprotein or more specifically DNA, which you probably have all read about in Time Magazine if you haven't read about it in your own books. Deoxyribonucleic acid, it is composed of four pyrimidines and purines. These purines and pyrimidines, which are much smaller chemical molecules are then conjugated to form and, and also sugar is added, ribose, and it eventually forms a very large molecule which is DNA. Vitamin B12 and folic acid are both catalysts, or co-factors, in the conjugation of the pyrimidines and the other, purines in the formation of DNA. If either one is absent or insufficient in the amount, DNA manufacture stops and the person suffers symptoms accordingly.

59:44 Speaker 5: [Unclear]

59:48 Dr. Bethard: The question was where is P-32 treatment given? Either in the hospital or in the office. It can be given either place where, it has to be given wherever the license says is to be given though.

1:00:00 Speaker 6: [Unclear]

1:00:01 Dr. Bethard: Pardon?

1:00:02 Speaker 6: Do you have to administrate it [unclear]

1:00:06 Dr. Bethard: Yes. The doctor has to administer it. [Bell rings]

1:00:12 Speaker 7: Is it possible at all for the body to store this vitamin B12?

1:00:16 Dr. Bethard: Vitamin B12 is not stored at any great amount. In patients who have pernicious anemia, if one dose is given that may be effective for 3 to 6 months. So there is some carryover but it's not, not stored say that so the one can get along with it from then on. Back there. I can't hear you. Pardon?

1:00:47 Speaker 8: [Unclear]

1:00:51 Dr. Bethard: Unfortunately, it does not cure it. It's a, it's one control measure and we certainly can make people feel better for a longer period of time. We hope that we've prolonged, we can prolong their lives, but that gets to be a statistical matter and we are not sure.

1:01:11 Speaker 9: Is this license issued only to doctors [unclear]

1:01:17 Dr. Bethard: The license is issued only to doctors and only to doctors who've had training in radioisotope use.

1:01:26 Speaker 10: What is the natural source of Vitamin B12?

1:01:32 Dr. Bethard: Most any animal protein, meat particularly, milk, cheese so forth. Before it became identified as vitamin B12, there was a deficiency disease in animals which was described after they had been fed purely vegetable protein and this was known as the animal protein factor, which turned out to be vitamin B12. Incidentally, I'd like to correct my answer to that first question, radioisotopes and licenses for their use can be granted to any type of scientist, biologist, zoologist who wants to use them in experimental animals. But for use in humans, only the doctors can.

1:02:21 Speaker 11: [Unclear]

1:02:30 Dr. Bethard: That also is, the question was how long does the benefit which follows the administration of radioisotopes to a person having leukemia last? That, it's quite variable, a person with a certain type of leukemia called chronic myelogenous may be benefited for a year or more. As the disease goes on, the length of time the benefit lasts will be less and eventually, he will receive no benefit from it.

1:03:07 Speaker 12: Are there harmful after-effects [unclear]

1:03:14 Dr. Bethard: Not in the doses used. One can give too much. It's quite possible to give enough to hurt the patient. No, the only, there's no harmful effect from the P-32 per se. The only difficulty is that the disease becomes unresponsive after a long, after a certain period of time and that period of time is variable.