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Some examples of the kinds of errors to be found in the transcripts are provided below.

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Dr. Bonte: Research

Well, uh, when I got out of the Armed Forces at the end of World War II, and looked around for a residency, the most attractive thing I saw was a fellowship offered by the atomic energy commission which had just gone public and had established thrree or four labs for medical research at university medical schools. They were offering fellowships to interested physicians who wanted to learn to use radioactive materials in medical research and treatment. The idea was that radioactive materials could be made to localize in cancer and within a decade cancer would be obliterated and that was honestly the mission of the atomic energy commission's medical research division. It turned out of course that cancer treatment was a very small part of what would eventually be developed out of what came to be known as n nuclear medicine. There are only a few cancers of minor importance that can be treated that way.
However what did happen was that radioactive matera materials evolved into a major group of diagnosticprocedures med-ical procedures. For the identification of disease factors processes ongoing in patients and in specimens derived from patients. And the full discipline which was sort of generated in those atomic energy laboratories has come to be known as nuclear meidcine. And it started out as a part of radiology and is more closely related to it because of common expertise in handling radiant sources.
And that's why many radiologists were involved in the birth of it including myself. I was then later trained as a radiation therapist but I never outg outgrew my fellowshi fellowship in the atomic energy laboratory, and I always continued to work at ne nuclear medicine, even though I worked part time for a long while in other branches of radiology.
When I came down here to Southwestern, there wasn't really any nuclear medicine going and and I came here in part.becaugse there was an opportunity to start ax a new laboratory from scratch. And I brought some colleagues and we developed a pretty good enterprise thex The department of radiology in general ultimately grew to the point where even though I was the chairman of it, I had a fair amount of time that I could devote to nuclear medicine reserch. And by this time I had developed a group of sophisticated colleagues, to help me in the laboratory and I had made connections with an equally sophisticated group of colleagues in other departments here at the school. One of the great virtues of Southwestern is interdisciplinary research, interdepartmental research.
Itmay be hard to imagine after spending some time around here, but in a number of medical schools the barriers between departments are like frontiers in the old days in the Balkans. There're literally patrolled by armed guards, and by George, onehad bette better not cross them. But they virtually do not exist here formany purposes, including teaching and research. And so its easy to find a gruop of talented people to work with who have a great variety of skills. And being associated with such a group is the secret ofstaying I xxxx staying acative in research. whhen you're spending major amounts of time in administratio-n.
Now, over the years our laboratory did a number of pretty good things with instrumentation and we evolved in the the directicn of studying the cardiovascular system and what could be done withit with nuclear medicine tests. And we developed several and they were found to be useful. but we got interested in estimating the blood flow to the heart muscle in health and disease.
And we developed acouple of research techniques for estimating and actually estimating in terms of quanity per unit-time, the amount of blood flowing k in the heart muscle, oh uh in first laboratory animals then in patients under examinations. And it became evident that we needed to be able to make pictures of the blood flow of the heart in healthy and

diseased states. We were aware as everybody is who works with nuclear medicine, that ~~radioactive~~ compounds can be made radioactive which will localize selectively in various disease processes. And we therefore began to look for a compound which could be made radioactive which would localize in damaged heart muscle. And we worked with one compound and another for several years, and we had only modest success in laboratory animals. But one day at a conference with some people from cell biology and pathology, a discussion started up about the metabolism of damaged, irreversibly damaged heart muscle. The proposition was that, in the course of arteriosclerotic disease suddenly the blood flow drops below the required threshold level, muscle cells become irreversible damaged, and they die, and a coronary or a heart attack is the result. If the volume of muscle involved is tolerable , the patient will recover , if the volume of muscle of is so large that the heart's pump function is damaged beyond the threshold point, then the patient dies unless he gets an artificial organ replacement or some such thing. So it seemed especially critical to be able to estimate in some direct fashion the amount of muscle that was damaged in a heart attack. The electrocardiogram gave some indirect reflections of the first the existence of damaged muscle and some hazy notion of how much was involved. Then over a period of years some chemical substances in the blood lent themselves to chemical detection, the amounts of them that were present reflected the amount of heart muscle that was damaged. This also might reflect damage to any other muscle as from an injection or wounds on the arm, the tests were not that specific. And so the cardiologists were still hard pressed for evidentce of the quantity of muscle involved and what significance this might be to the heart. And this general area was under discussion at a conference at which one of the pathologists mentioned that a former member of the department here studying irreversibly damaged heart muscle, and knowing that the element calcium rushed into damaged muscle cells in supernormal quantities, and wondering why this happened, chanced on an observation. The observation was that calcium containing crystals that looked something like the matrix in normal human bone were often found in irretrievably damaged cells. And at this point I was struck by the fact that this give us an avenue towards depositing selectively a radioactive material in the damaged muscle . Because there's a family of phosphates which are related to ordinary laundry detergents. These phospates can easily be labled with a radioactive element which emits radiation of the sort useful in making pictures, a common method of testing in nuclear medicine. So I , as soon as the conference was over, as a matter of fact I got out it as soon as I could and called the laboratory and told them to set up an experiment of the sort we had done so often before in which we generated a heart attack in several dogs. It was a well known technique that we had perfected many years before. And when there was obvious muscle damage a day later, I caused the animals to receive phospates labled with this element, technetium 99M which emitted radiation. We made pictures using the technetium radiation and not only did we see the phospate in its normal location in bone but there was a big star shaped image of the damaged heart muscle. And that began a research program that's now culminated in sixty or seventy papers and a test that we've done four thousand times in the coronary care unit at Parkland. And it's being rather widely done around the country, and I gather from what Dr. Stokely told me yesterday about an international meeting he had come from it's widely used in western Europe and Japan as well. Well one would expect this because it works, and it does for the first time give the picture of the amount and location of damaged heart muscle in a heart attack. And it is a useful piece of information to have, it's not critical, it isn't going to save the world,

but it's a neat new test. And it has all sorts of implications in the research laboratory. It gives you a tool to use in studying heart attacks, it uh and especially methods to prevent or to treat them once you know vessle closure has occured. The search... we're still searching for better drugs than the ones that we have been using , but neither we nor anybody else has come up with anything better than the labeled phospates and a new family of drugs may be identified at some time, but for the nonce and probably for the next five or years or so everyone will continue to use labeled phospates, to identify damaged heart muscle in a heart attack. The test is one intended to be done at the bedside in a coronary care unit, using a mobile radiation detector, which ' will assemble the radiation it sees into a picture. And the picture becomes available immediately to the physicians at the bedside. And uh we can cause, without moving the patient can cause pictures to be made in two or three different projections. Various young people in our organization are working on computer programs designed to tell the cardiologists in terms of grams orce's how much heart muscle is involved. this can be done with some, if the picture's good enough.
? was the detector developed specifically for this test?
Nxxx
No. The detector's standardized, somehow Bob and Ann have gotten the idea that the detector is the important thing. The detector isn't. The detexx detector is widely xxxxxxxx commercially available. However mobile ones designed to be used at the bedside really weren't available before. But the development of this and some other tests for imaging the heart has caused manufacturers to make mobile lightweight systems to be used at the bedside and they've sold hundreds of them now, to do tests of this sort. But we didn't invent it. And it's a secondayr development to the to the uh, it's like seatbelts there' wouldn't be any if there weren't automobiles.
So the instrument is not the important thing. It's the concept of being able to see on a picture the amount of heart muscle that's irreversibly damaged.
I want to point out that this is not the greatest piece of research that anybody has ever done. it isn't even the best thing that I've done. But it happens to beone of those things that's eyecatching. It's like anything that Jackie Kennedy does, it's eyecatching. And for some reason or xx other we no sooner had the words out of our mouth at the first meeting which we reported on xhxxx couple dozen cases three months after I had made the first observation involved and suddenly all thx over the country newspapers areprinting the words as if the messiah had returned again. And although it's intriguing it's not one of the great research developments even at this school. I consider things, xxxx like Gxxxxxxxx what Goldstein, Finklestein and Unger have done to be a formidible basic ocntributions to medical knowledge.
?Was the development of this test at all in line with what you had been anticipating when you began to look for a compound?
Yes, this did exactly what I had been xxxxxxxxxxxxxxx hopeing to find a compound to do. What the meeting did was to provide me with a biological mechanism that I had n't thought of before. Involving a transport of calcium ions.
?How much longer might you have looked if it hadn't been for the meeting?
Oh well we'd still be looking.
?Was your plan taking you in that direction?
NO. Nobody could, including ourselves had thought of calcium and phospate ion imbalances as the apeture through which one could leap to being able to image damaged muscle. It turns out, now that we know about it , you can image all

bruises
enlarged


sorts fo damage muscle: burns, brusises, crushing injuries, auto accidents and so forth, and not just the muscle of the heart. Muscle of the rest of the body will respond the same way. And people we know are studying electrical and traumatic burn and so forth to see whether they can quantitate muscel damage.

?Dr. Dowbin was speaking of blood calcium, how does it tie int?

Yeah, phospate is involved in the energy utilized for muscle contraction and calcium is involved in the matabolism of phospate, and also itself in muscle contraction. A lot happens when a heart attack occurs, the oxygen level in tissue goes down to the point that cell death results, and the cell membranes which are usually selectively permeable to various ions suddenly become much more permeable , uh they become porous and calcium flows in in great quantity and phospate accompanies it. And there's a great deal more exchange ofxxxxxx calcium and phosphors going on than is evident just by the crystals that the pathologist saw and which caused us to experiment with this. That turns out to be a small fraction of the total volume of calcium and phosphors involved. However it was enough to get us started with looking at the process and ultimately labelling it so that it can be used for medical diagnosis.

?Previous to the conference were you confident that you would eventually solve this problem?

No, because others and ourselves had been working on it for fifteen years and we really hadn't gotten much of anywhere. There were some agents that xxxxx would give enfeebled pictures if one took the heart out of the subject animal and filmed it over a period of half an hour and this was a sort of a dim light in a wilderness. But we did not have reason to suppose that there was lurking around on the shelf an agent commonly used in diagnostic nuclear medicine that could easily supply the answer. Why nobody had seen this before while studying the skeleton which one does daily with labelled phospates, you would think that somebody somewhere would have xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx incidentally in doing that test on a person who had recently had a heart attack or had so much heart muscle damaged that he accumulated this material. But if it occured nobody made the observation.

? Is there any likelyhood that that line of xxxxx investigation would have been abandoned ....?

Oh well, there are other ways to do it . You can give one or another of different radioactive drugs that localize in the heart muscle that blood still reaches and from the holes in that pattern you can deduce where heart muscle has been damaged but you can't tell when. As a matter of fact all you can safely say is that blood, and therefore the radioactive agent that it carries, is not getting to that part of the muscle. So you can't say why the hole is present. It could be a scar, the result of a heart attack ten years ago. Or one a day ago or muscle that is not irreversibly damaged. We were also working in that direction and still are.

? You said that this wasn't even the best piece of research that you had done ....?

Well, the , maybe the best thing that we've done is a very complex business that does involve instrumentation. Long ago, fifteen years ago, we were the first people who put information from radioactive pictures on magnetic tape so that we could process this with a computer-like program to extract information, the real information, out of it and discard data that were not contributory. In those days, the drugs that we used to emitt the radiation did not localize very precisely, thexxxx the instruments we used for detecting it were crude, and you had a hell of a time make making anything xxx out of the picture. And it struck us at the laboratory that I came from, that it would be a good idea to record xx everything the detector saw on magnetic tape and then computer process it , in essence, to extract the real information from the false information. Such as is done let's say with transmitted lunar photographs. You know they're computer processed to clarify the detail. And we had the first fast data processing system that anybody ever built here. Cancer Society grants helped us to do this. God, it was a crude, xmassivexx massive old machine! And it didnx didn't actually use a computer, but it used a similar circuits to process the information. And of course this is now one of the common modes of handling picture information in nuclear medicine. You record it on tape and process it in a variety of ways to sharpen up the picture. But we did some of the early work and I think scientifically this is a better piece of work maybe than the hearxxx heart muscle imaging test, but gee, who remembers anymore. It's so long ago and there are so many layers of information built on toxpxxx top of tx this that sometimes even I forget that we worked on it.

?What was the conventional method of recording information then, just a graph paper recorder?

Yeah, the conventional method of recording was with a solenoid that was activated by a little currents feed to it by the detector which was a small crystal of a particular sort that emitted ligth when it absorbed a pulsxxx pulse of radiation adn and it put out a small electric current. The current was amplified , driven into a solenoid which was activated, and the core of the solenoid acted as a tapper, and it tapped txxx through carbon paper onto a sheet of tissue paper. It would make a visible stroke whenever itx say xp a particle of radiation was discovered. Your picture xconsisx consisted of a mass of strokes accumulated by the detector that scanned back and forth in a square or rectangular pattern, in a plane parallel to the patient's body. And boy, sometimes it took a lot of imagination to make a meaningful picture out of all those dots on the tissue paper. And we were seekx seeking to resolve the picture out of a mass of true and non-contributory information . That's why we decided to put it on tape and to process it various ways to get rid of background stray radiation and so forth.

?From other interviews it seems that's a characteristic of research today, to identify the relevant information out of an overwhelming mass of data?

Trying to see the true picture through all the flxxxxxx false information. We just happened to be in a situation where we were actually working with a picture, but the principle is the same.

? It stkx strikes me that a more conventional type of research is what you described as the discovery of the heart scanner test: "Eureka, I found IT!"

Yeah that's the light bulb approach, where it all of a sudden turns on.

?But much of what I've heard suggests that the information is in there someplace and the researcher's problem is to identify it.

xx That's correct. That happens to be the case, and you try to sort out the real signal from the noisx noise. And then to amplify the real signal and add to it. And honestly you have to be lucky to make a quantum jump in your work as we did when we set up the phosphate experiment. Before that I had been working 20 years without axx any quantum jump. And expect that as long as I continue toxx to work I won't get that lucky again xxxxxxx. But you know it's fun when it happens, but it does not nesessaxxy necessarily mean that the observation that you've made is more valuable ~~thatxxxluablx~~ valuable than what you've done before, or what others may have contributed to thix the solution of the problem.

? Then it's not the thrill of the quantum jump that you're working for; all internist

your work contributes something?
Yeah, and we've done you know, gee, I've publisheda hundred twenty papers or something like that. Many of which contain little bx bits of information that may lie faxxxxx fallow for many years, and but may ultimately turn out to be what somebody else needs as a piece in, you know, trying to form a picture out of his sea of signals and noise. I know for a fact that a number of things that I've done have latter been utilized by other people who make much more significant observations than I did, well that's true of anybody who's pxxxxxxxxx productive in research. And conversely when we identified a test for labelling heart muscles fxxxx so that one could make a picture out of it, I was using and observation made by some good friends of mine at a laboratory in New York. They first learned how to put radioactive emitters on detergent. They weren't looking for a heart test, they were looking for a bone test and they developed a marvelous one. It's a beautiful piece of work. But we couldn't have done what we did without what they had done xxxxx before. And armed with the compounds thx that they had developed, I was confident that presented with this mechanism that we could make the pictures that we did. So that, as you say, it all fits together. and hardly any investigator has the chance to put the whole thing together from scratch. Always using utilizing information generated by somebody else.
?Describe your work in relationship with your colleagues?
Well, therrare, I would say, oh anyway 15-18 people working on various aspects of imaging of hxxxx heart attacks, and there are three amjor people among them. One is Bob Parkey, who is my successor running the nuclear medicine laboratory. He trained in our system and grew up in it, and has participated in this research from the first day. He and I stood there together looking at thxx the first picture. He also hxx has special training in computer technology and imaging. And has done you know a lot of original work along tx those lines himself. Then, a key member of the team is an internest who's a cardiologist, Jim Willerson. Willerson runs the coronary care unit at Parkland Hospital and it's Willerson's patients who were utilized in the test. Willerson was about the second man to see the picture and he immediately realized its implications for the mxxx management of patients with heart attacks. And he organized the clinical study after we had done the required laboratory basic science for it. Then we were fortunate in adding a young pathaologist by the name of Max Buja, who is a cardiac pathalogist, and he specializes full time in cardiac pxxxxxxx pathology. Through Max Buja we study the mechanism of localization of these drugs in damaged heart muscle. And Buja has learned more about this process than anybody anywhere else. Without these three people none of us could have gotten as far with this as we have done. Then there's a formidable group of about a dozen and a half young individuals in five or six departments who've explored one ofxx or another avenues of this problem, under either the general supervision of Willerson, or Parkey or Buja, or some combintation of them. Now, I review what's going on with Willerson, Parkey and Buja, and we have lunch periodically and they tell me what's going on and where the problems are. And I make suggestions, "Why don't you do this", "why don't ux you try txxx that." And if everybody thinks it makes sense, they go do it. . And once in a while it works. lixx So, I keep in touch with thingsx the thing and I probably see Willerson xxfx oftenest of all of them, because being the clinician he has maybe the best overview of what's going on. Yet he's pxxxxxxxxx profoundly grounded in the basic sciences and he knows a hell of a lot about nuclear medicine by thisxxxxxx time too, as does Max Buja becausexwxxx of his contact with it. And we have other valuable people,

biomedical engineers Earnie Stokley; David Mishelevich and his people all are involved with some aspect of this research. And it's supported by a center grant from the National Heart and Lung Institute, Soon after we identified this, we got together and decided that this and a few other things being done around here were important enough to try for a new center program that the Heart Institute had announced in the area of myocardial ischemia or low blood supply. So we put together a proposal of which Willerson served as the moderator or principle investigator. A great group of people visited here and heard our proposal and they funded our research center here and the study of the physiology of heart attacks. And because of the availability of funds trainees have collected around the program and it's a major research enterprize which, as I say, involves six or eight departments. And it involves some people I've never even met because they're three steps remote from me. Every once in a while I see somebody delivers me a paper, and I'm now down about six or seven from the authors with Willerson near the bottom, and here is some young fellow who's made an observation in this field and I find out about it when I review things with Willerson and Parke. But there's a large group of talented people now at work and I keep in touch with them through the top.

?It seems to me that yours separation from the lab must provide some essential sort of different perspective?

Yes it does and as a matter of fact it , there's a lot of detail going on that I'm no longer aware of and that's the one thing that bothers me the most. When I was working in the laboratory before, I knew everything that was going on. And you know, I was constantly trying to keep pieces that fit and throw away pieces that didn't fit. And we'd organize little excursions down alleys that turned out to be blind. Well I don't even know about some of the alleys. But every once in a while I find out about 'em and you know others, I find, have not identified them as alleys. So I talk to Willerson and Parke and we organize a little excursion and sometimes you know there's a lamp at the end of the tunnel and other times a rock wall. But there's no substitute for it, because I spend 95% of my time in administration, which goes with the job.. But I have a rare opportunity to remain active in research.

?That's an awfully graphic description of the sense of investigation ....?

It really is. See, there are tunnels that come to blind ends, there are tunnels that taper down to such a tiny aperture that you find you can't get through them. You don't know whether there's some big cavern or something on the other side or not; once in a while there is. And others a tunnel will narrow down and suddenly will blossom into something productive, a whole new series of caves.

?You have a very physical sense of your work..?

O yeah, I know where it's all going; what the ultimate outcome of it all is I really don't know. But what I do know is that we've discovered an interesting way to look at some of the processes that go on when heart muscle is damaged in a heart attack. It turns out that you can use this process to make pictures too which is , I think, the feature of it that captured public attention. Whether it should have or not I don't know, but you know how the media work these days. There's a constant struggle going on to find something new, topical, interesting, not previously described and so forth..