Department of Surgery History Interview
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This interview presents Dr. John Grant, Director of the Surgical Nutrition Research Laboratory, Department of Surgery, Duke University Medical Center. The subject of this interview is the work of this laboratory and Dr. Grant and his background. This interview takes place in the Deryl Hart Conference Room, Department of Surgery, Duke Hospital South. Your interviewer is Dr. James Gifford.

Dr. Grant. Perhaps, we might begin by having you say a few words about your own background and particularly how you come to have the professional interest that you have and how you arrived at Duke.

I began at the University of Chicago Medical School when my current interest began then when I encountered a Dr. Prohaska there, who was a generel surgeon but he dealt a lot with patients with inflammatory bowel disease. He sent me to a Dr. Stanley Dudrick, who at that time was at the University of Pennsylvania to learn a new technique called intravenous feeding. In 1967 was the year that I went to the University of Pennsylvania. We spent about a week there at which time Dr. Dudrick was doing primarily his dogs. We saw that kind of experimentation going on with intravenous feeding. And we saw two of his patients who were being fed intravenously. I, and another medical student carried that back to the University of Chicago and began to do intravenous feeding in the Department of Surgery under Dr. Prohaska's oversight about in 1967-1968, on a couple of patiemts who had Crohn's disease with fistulas that really weren't surgical candidates, and both of them survived our intravenous feeding and ever since then I have been deeply involved with nutritional support of surgical as well as medical patients both in and out of the hospital. Toward the end of my medical school career, I became interested in a surgical program for training of academic surgeons and among several others, I was very interested in Duke University, and made application, and a Dr. George Block, who was a friend of Dr. Sabistons wrote a very nice letter of recommendation, and I was accepted in the Residency Program in 1969.

Can you say something in general why the study of nutrition is important for surgery?

I think that 1) surgery is a very stressful mode of therapy and if you put surgical intervention on top of malnutrition, patients do poorly. There wounds heal less readily, they get more complications of infections and in general, have more organ dysfunction such as cardiac failure and renal failure in the postoperative environment. If we can intervene preoperatively and replenish these patients at least to some degree, there complication rate seems to be lower. If we are called after surgery when they have complications and can't eat and intervene, then we think that the subsequent incidence of complications can be reduced. So, the use of intravenous feedings when the patients cannot eat or should not eat, is felt in general to improve patients responses to various stresses, not only surgery, but chemotherapy, medical therapy for patients who have medical illnesses, tiding them over and helping them to respond to their disease, at least until they can eat.

Can you say something about what a Surgical Nutrition Research Laboratory is?

This laboratory began in about 1979 after I joined the faculty, when we became interested in doing research trying to promote intravenous feeding. We still have many problems with it. The form of feeding we provide gives everything intravenously and there are many questions as to what needs to be given. In an oral diet we get a poupouri of everything and humans do well. When we begin selecting out of that oral diet what should be given intravenously, somethimes we do not know. So we began the research protocol looking at animal models to study various substrates to determine which ones would help if we gave them intravenously. Two of interest that have been through the years being evaluated are glutamine which is an amino acid and it appears to be a specific fuel for the intestines. It is currently not provided in intravenous formulations, and patients who are given intravenous feeding in the preoperative or postoperative or hospital period, generally undergo gut wasting. Their intestines are malnourished because they are not getting calories. The intestine does not like to burn glucose. So, we

may be treating a patient with a fistula, for example, who needs to have healing go on in the small bowel in order to close the fistula, and yet we starve it. So, again we are looking now at providing glutamine intravenously trying to give this fuel for the gut. Other fuels we are looking at specifically are directed toward treating patients with stress. In the stress situation, there are different amino acid profiles, different energy substrate utilization profiles, intolerance to glucose and we are trying to formulate special formulas to assist in the stress patient. Another area of research interest has been trying to develop nutrient solutions both intravenous and enteral which can assist or stimulate the immune system. So, once again, we can assist the patient in preventing infections and complications of surgical or medical intervention. So, the research was begun because of questions that were unanswered in the field of nutrition. What can and should be given intravenously to optimize patient care and we are still answering questions that keep coming up. Trace elements are another area where we have done some investigation and we have little idea about nutrient needs for trace elements when given intravenously, and vitamins are another one. Of particular interest now are carnaging which is useful in fat metabolism, which is one the energy substrates we give during stress. So. the research laboratory was really designed to try to modify the intravenous support and the enteral support to optimize patient outcome.

Was there any of this work going on at Duke before your arrival?

No, in fact intravenous feeding wasn't begun at Duke until I came as an intern and that was about the time when most hospitals were beginning to develop programs, around 1969, 1970, and at that time another resident with me, an intern by the name of Al Gerbin, who is now Chief of Trauma, University of Virginia, he and I began the program here, of intravenous feeding. I remember in Halsted Ward, we used to get a vacuum glass bottle and add each thing individually to the bottle. It would take about an hour to prepare a solution for a patient, and he and I would do it every night and hang the bottles. So, nothing was being done here until Al and I began it in around 1969 and then, it wasn't until I came on faculty that we began doing the research work in 1978-1979. There have been other people interested in nutrition obviously, and Dr. Kaymin is a nationally and internationally known individual in Medicine who has done a lot of work with vitamins

and some minerals, so there has been work in nutrition, but not specifically in enteral and parenteral nutrition which is where the surgery department is specialized.

How was your laboratory supported?

In the first years I began it, it was with NIH funding. We had a research study to evaluate the nutritional, well let's see, it was called, The Changes in Nutritional Parameters of Patients Undergoing Chemotherapy for Various Malignancies. Our interest was to evaluate them at the time they began their chemotherapy. What is their nutritional status? What is the body composition?, and then, to give them intravenous feeding or not, and monitor their response to it. What happened then after the course of chemotherapy, or perhaps several months later. So, we began the laboratory with NIH funding. Since then most of our funding has come from various companies who are very interested in developing products so the animal work has been primarily supported through private industry support grant money.

Let me ask you to refer to the titles in this previous summary of your laboratory's work, and explain each of them in turn, beginning with Why This is Being Done from the Point of View of Surgery, in the terms about which you spoke, earlier.

The first title was: Adaptive Response Following Massive Small Bowel Resection. Patients who have undergone near 90% or 95% resection of their small intestine obviously have a problem absorbing oral diets. These patients have been placed on home intravenous nutrition, receiving all of their nutrients in the home environment, usually at night and going about their way without any feedings during the daytime, eating what they can. After we did this for some time, we found that in the period of two to three years, some patients required less intravenous feeding. If we maintained it at a steady level, they gained weight. So we began tapering off the TPN, and it was apparent that the small bowel in some way, even though it was very short, was adapting to the resection. They were gaining more function with the residual bowel. And we did some animal work at that time,

and others have done it likewise, showing in the animal model, a similar process. The gut would elongate. The gut would increase in its diameter, and if you did a histological section, the absorbative surface actually increased, it was not simply stretching. We have been following now some home intravenous patients with short bowel syndrome for just over eight years, bringing them in periodically, usually every six months to a year, doing absorption studies, doing x-ray series, doing some bowel biopsies, trying to evaluate this adaptive process, and indeed, in all of our studies, we found that the adaptation that occurs, occurs primarily within three years, and that's about it. We are still studying some patients, trying now to add glutamine to their diets and see if that's going to result in more adaptation, since its the fuel of the gut, so the studies are ongoing. Our conclusion from the studies is, in general, that we can now approach a patient who has had a massive small bowel resection and tell them that it will be at least three years before we know whether they are going to need to be on intravenous nutrition permanently, and we hope that they aren't. So it gives them some hope, based on some research that we have done. There is a group now up in Boston, Doug Wilmore, who is starting a massive study now in the adaptive response after massive small bowel resection, where he is hospitalizing the patients for an entire month and giving them special nutrients and we are beginning to look at this here, too, trying to establish a satallite part of his study. So, patients would be brought in and put on these specialized diets both intravenously and orally attempting to establish the optimal gut adaptation, the most function.

Where is Dr. Wilmore located?

Brigham and Womens Hospitals in Boston. He is one of the leaders in home intravenous nutrition, both in research and practice.

Studies in Morbid Obesity is the second title and obviously when you are in nutrition you get into both ends. One of them is with the malnourished, wasted patient and the other is with the overeater, and particularly, how it interfaces with morbidity and mortality. We have done no research in outcome studies, as far as what happens, but I would be very interested in what surgery would have to offer, and I am particularly interested in the super obese, the patients that weigh 400, 500 or 600 pounds. For these patients, really there is no medical management, no

dietary programs that are effective and there have been no surgical program effective. Over the years, we have evolved an operative procedure specifically designed for these patients, and it ties in with our earlier research in that what we are doing now is creating short bowel syndrome in the patients. We take them to the operating room and bypass all but about ten inches of their small bowel, attaching that ten inch segment to the colon, so that whatever they eat has very rapid transit. They have diarrhea if they overeat and they have no absorption of any of those nutrients. So, in these patients, we create what we are trying to treat in the skinny patient with short bowel syndrome. We create a situation where no matter what they eat, they must lose weight, then we integrated that, the anatomical setting for weight loss with our intravenous feeding of the patients that have short bowel. So the whole protocol is to operate on the patient, to create a short bowel in an anatomical situation, place a home intravenous catheter, but instead of feeding them everything they need to maintain their weight, we simply give them only proteins, vitamins, minerals and fluid, so we restrict the caloric intake. So, we can avoid all the complications of starvation by providing all of the nutrients and none-the-less obtain weight loss. And that was just published, too, and I have a handout here of our publication on it. So, this is a unique surgical procedure that has been developed at Duke University Medical Center, Department of Surgery, that probably is, at least from our experience, a very effective and hopefully will be widely utilized method. In that super obesity study, then, we are interested as patients lose this tremendous amount of weight, some of them 300, 400 pounds. What happens to everything? What happens to muscle function? What happens to liver function, cardiac function, gut functions, so the research we have is to admit these patients to Rankin Ward prior to their operative procedure, at the end of their weight loss program, and then one or two years later. And we do a whole series of tests looking at gut function, liver function, pulmonary function, cardiac function, and to date, indeed, we found all of them to be better, as you might expect with a massive weight loss organs tend to function better and we hope that these patients will maintain a longer life span because of their weight loss. But that is a long term study.

Is there any relationship between the theory behind your surgical approach and what Dr. Kempner did for so many years with his rice, in a

sense that he was restricting by keeping patients to a very minimal rice diet. He was taking control of caloric intake and measuring very carefully day-by-day to make sure that nobody cheated, etc.. Is this a surgical approach that is parallel?

It is very parallel and the concept is no calories, you are going to lose weight. The problem with the Kempner studies, he really did not look at function as much as we are and no one knows from all of his studies how dangerous that was, because they did not do liver function testing, they didn't do cardiac function testing, as much as we are doing. The other down side of what he was doing was that recurrence of weight loss was common, once they got out of the program. Then, again, the process of losing weight is maybe not a big deal. Anybody can do it. There are ways to force patients to lose weight, whether it is the rice program where you are under direct observation and an iron hand, or whether you have a surgical procedure which forces. There can be no cheating with that one. But once they get out of strict control, that's the problem. What we do at the end of weight loss when they achieve their ideal body weight, and that's what we're shooting for, so for in men 190-200 pounds for the end of the weight loss program. What we do then is to reoperate on them, take down their bypass so their anatomy is normal, then we construct the commonly used gastric restrictive procedures for morbid obesity. Either a vertical banded gastroplasty or a Roux-en-Y gastric bypass, both of which have been around for many years, both of which are known to be effective in losing weight if you are only morbidly obese, 100-200 pounds overweight, the concept being that this would help them keep the weight off. So, the real research now is the long term study if we operate and we follow them now for up to eight years to see if they would regain the weight over a period of time under minimal supervision and so far that has worked. So, there is a little difference in what each program accomplishes.

I seem to recall that there were some patients who were stapled who gained weight anyway. What happened there? What percentage of patients gain weight after stapling and does your research suggest anything about why?

Most of the poor outcomes were from the horizontal gastric stapling procedures which have all but been abandoned. The staple line would break, the hole would enlargen, patient's would essentially lose the restrictive gastric pouch over a period of time. It would last up to one year and then it would stretch and tear, and then destroy the operative procedure. So then two other operations became available, one by Mason, and one by Dr. Flories, and these are better stapling devices. They have reenforcing procedures so they don't break down, so the results from these two operations, the vertical banded gastroplasty and the Roux-en-Y gastric bypass are much better. About the average weight loss is half of the obesity. So if you are 100 pounds overweight, they will lose about 50 pounds. The mainten-ance of that has been followed for about 8-10 years and it has been good. There have been some recurrences, some will regain the weight, some that lose to ideal body weight. About 85% of the patients have an excellent result and maintain the weight loss. So, there have been some changes in the surgical technique that in the last 8-10 years seem to be working much better. Still not an answer to obesity and obviously research needs to be done as to why are we overeating. and I am not in that area at all. Dr. Pappas is doing some work on that when you talk to him about appetite, and I think neurosurgery is doing some research on the center of appetite. I am not involved with that, but the surgery department is. When we resolve why we overeat, we won't need surgeons. We're trying to patch up the work right now and I think for the morbid obese I think the standard operations are fine and I am For the super obese we are still doing this ongoing study, and until I get them out in ten years, I am not too happy saying how effective it is. So far it has worked nicely.

The third area of our laboratory research has been in the effects of argenine supplementation and glutamine supplementation to intravenous feeding, and this is primarily a rat study. Both are amino acids and both are considered as a protein substrate, but more recently we recognize that argenine as an amino acid is a critical fuel for the immune system. So, lymph nodes, the thymus, lymphocytes are very dependent upon argenine for their activity and function. If you make a patient or a rat argenine deficient they have a very marked difficulty in responding to any septic or stressful response. So argenine deficiency can be lethal in the stressed, infected or challenged human. Glutamine we have already talked about a bit, and

although it is an amino acid and thought to be a protein substrate, instead it seems to be primarily a fuel substrate, and it is a primary fuel for all of the gastrointestinal tract but primarily the small bowel. If the small bowel does not get adequately fed, it atrophies, the mucosa thins, and actually if you look histologically, the spaces between the cells increase, and we have found experimentally, at least, that if you put bacteria into the small bowel that is malnourished, that these bacteria can move right through the gut wall into the blood stream and into the lymphatics. We call that process translocation of bacteria. The concept, then, of patients who are critically ill and in the intensive care units, who are fed intravenously with 5% dextrose, that over a period of 3-7 days, this gut atrophy occurs, and as it occurs, you begin translocating either viable or non-viable bacteria, and/or with their toxins, and its this process of either infection or toxins that get translocated that causes a dramatic worsening of their condition. And indeed, we think it is one of the tripping mechanisms for multiple organ failure which has about an 80% death rate in our intensive care units. So, the concept that we have and the question we are asking is, if we supplement with argenine to support the immune system and with glutamine to support the intestinal tract, can we prevent the gut atrophy and the immune depression and therefore, decrease the incidents of all of the complications in critically ill patients. The model we have is a rat where we feed them intravenously or enterally with products that do or do not contain glutamine or argenine and then subject them with an interperitoneal injection of E-coli, and that organism was obtained from the blood of a human who had a pelvic abscess of E-coli. So, it is a bug that ruins humans and causes critical illness in the intensive care environment, and the results to date have been very impressive. Glutamine and argenine combination in either enteral or parenteral products seems to dramatically reduce the death rate in rats subjected to this challenge with E-coli. We are now modifying the amounts of each one trying to find the optimal ratio between the two and that's what the ongoing research is concerned with. Once we find that answer, then obviously transition to humans will require more research because the rat is not like a human, but we have a start.

The last study was really in collaboration with Dr. Pappas and that was trying to address the observation that patients who are given intravenous feeding in the hospital lose their appetite. We do not understand why. The reason this has

clinical significance is that we feed a patient with intravenous nutrition, the are getting better, we offer them an oral diet, and they don't eat. So, it's the transition period. The clinical practice has been to stop the TPN, send them home and hope they recover their diet, which, for the most part, works, but if we could block whatever it is that suppresses appetite, we could improve, and perhaps enhance the patient's recovery. So, he is looking at neuropeptide-Y receptors in the brain of the rat and I think you need to talk with him to obtain more of the research data, but in essence what we are trying to show was, does intravenous feeding augment or suppress these receptors in that these receptors, we know, are directly related to appetite. I have not been involved with that research other than assisting in the animal model which we already had going and providing some consultative work on how to do it. But I do not know the results of that yet.

So, these are the ongoing research efforts in the lab at the present time.

Let me switch to the Departmental level for a moment. Dr. Sabiston's Department has the reputation for being unusual in its attention to scientific research related to surgery. Can you tell me why you think that is and why it succeeds?

I think it is expected. When I came on faculty, the selection process, at least from my viewpoint, was that he wanted people who had all aspects of academic surgery under their belts. In other words, they were very interested in clinical practice, and improving clinical practice, they were very interested in teaching residents, and right on same level as important as those two, very interested in doing research to improve surgical training and surgical practice. So, I think it begins with Dr. Sabiston's selection process of people to bring on faculty. He is always looking for somebody who has an expertise which will add to the overall care plan. In my case, I guess it was surgical nutrition which nobody else had to offer at the time. And other people are selected for their transplant expertise. But whenever he interviews us or talks to us, it is always how is your practice and how is your research going, in the same breath. So, I think it has always been just part of the program. Expected and none of us question it.

And how do you think he came by that vision or that view that these things should be co-equal?

I think that is his philosophy of surgery. I think he thinks you cannot do surgical practice without being interested in questions of surgery and changing them. He was raised in the Halstedian tradition which has always been, if you have a question, address it in the laboratory and then transfer it to the patient.

Now, you used the phrase Halstedian tradition. In the first half of this century when Dr. Halsted's residents dominated American surgery, surgery was primarily clinical. I understand that to mean that surgeons approached their tasks from the point of view of improving their technique and their procedures, and that everything else related to technical questions and they worked back that way.

I think that's an excellent summary of that approach, the Halstedian approach to surgery.

But you just pointed out that Dr. Halsted also did emphasize the relationship between laboratory and surgery. How was the Halstedian emphasis on laboratory different from what we know today?

I'm not sure I know the answer to that. That's an excellent question. The problem I have is that all of my concepts of the Halstedian principles have been taught to me rather than experienced by me.

What do you understand by Halstedian principles?

Basically, that patient care is the first priority, and that everything else is subjugated to patient care. But to provide that patient care, you have to have all aspects of being a physician or surgeon. In this case, you have to ask the questions. If you have a question, you have to research it Meaning whatever, library research if has been published, or developing a research protocol, performing it, drawing the

conclusions and then returning to the patient, and then teaching it. All of those aspects.

It is clear to me that I have to understand where the difference lies. Dr. Hart, for example, who was one of Dr. Halsted's last residents, did not consider himself a researcher. He did a very interesting applied research that won him a lot of prizes for his development of ultraviolet lights in the operating room and he had sort of an avocational scientific interest in that he studied reproduction to the point where he could pretty well guess what sex a child was going to be when it was born. The monument to that, of course, is his home, but he did not consider himself a researcher and he hired Dr. Beard to be the embodyment of the pure researcher in the department. He recognized that most of his people were going to be busy building a new institution and doing the Halstedian thing of patient care first, and teaching and improving, and research was going to be down here and it is Dr. Beard who's work on virology, the bird studies, more or less evolved into something like the tree we have today. But the question I really have to wrestle with is what is the difference conceptually and practically between what Dr. Hart and men of his generation, understood research to be and what it is now understood to be, with Dr. Beard as sort of the bridge figure.

I don't know whether I can help you there.

What is happening in these interviews is, as people say things to me, things occur to me, and I try to get them on the table so I won't forget them. It is very clear that Dr. Sabiston is a different bird from Dr. Hart. Now, part of that is environmental. Dr. Hart said that in order to be a good Chairman and have success, you had to have an appropriate ratio of freedom and resources, and Dr. Hart would go on in his world to say, and since resources were always slim, the whole thing was built on freedom. And he operated as an independent contractor doing what he thought was best for the Department in the Halstedian tradition. Dr. Sabiston comes along in a different era when resources have increased and freedom, theoretically,

decreased by controls that come with the outside money. And he becomes not so much an independent contactor, as a broker, who is more-or-less charged to keep tract of the field and look for people who can come here and prove as you said earlier, the omomentarium of the Department, but at the same time are able to attract the resources to support that expansion. And he is doing a different kind of thing. Whereas Dr. Hart saw the field of surgery as divisible and gave over with complete freedom, parts of surgery to new men to lead, like Dr. Woodall in Neurosurgery, etc when the clinical workload got to a certain point. Dr. Sabiston has this global vision which I think comes from the fact that all of his mentors wrote the basic textbooks in their field. He has about six of them, and the common denominator is that they all wrote the basic textbook, and now he writes textbooks galore. I am trying to sort out in my own mind what it is that distinguishes the two eras. I will be grossly derelect if I try to argue in some way that the earlier men did not pay attention to research, but clearly the research they paid attention to was different. And part of that is the availability of resources, part of it is that the Halsted tradition is a vertical tradition, and the new tradition is a horizontal tradition. I just trying to see if there is anything else.

There is something to this availability to resources. Since I have been here in 1969, he had already established by that time, the concept that every resident would do research. And two to three years of research. Break their training period. And at no time was there a question of funding. It was always available. And if the resident did not get his own protocol which we were encouraged to do, then the attendings that we were associated with, would have a protocol. If everything failed, Dr. Sabiston had available money that he would fund the research. So, he had the resources to make this a part of the program. There was no question that you would do research and it was a rare resident that got through the program after talking to Dr. Sabiston, without doing two or three years of research. So, it has been a part of the program since I have been here in 1969. It is just expected. You cannot be an academically-trained physician without having done basic research in the laboratory. It is an interesting ability that he has had to make that a part of the program. I guess because of resources.

I began my interview series thinking that the two eras were going to be markedly different. It may be that I am going to come up with a thesis that one completes the other and that what Halsted began, and Joe Beard later became the exception that proved the rule, then the rule became the rule, I don't know.

It may well be. And it could be that the concept that Dr. Hart had was that you can't do research yet, because we are still building. I think that he and Dr. Sabiston would differ very little in the concept of how important research is, but it is the ability to perform it that has distinguished Dr. Sabiston in his era.

I usually end these interviews by asking my interviewee what question I failed to ask that I should have asked in order to fully understand what you are doing.

You have covered most of what I had written down. I think that's about it.

Thank you very much for your time.