ANDREW CONWAY IVY, M.D., Ph.D.

AN ORAL HISTORY

Recorded by

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ILLUSTRATIONS

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FORWARD

This is the third in a series of oral histories undertaken by the American Gastroenterological Association to document the history of gastroenterology in the United States. This 5 hour interview was conducted in 2 sessions on November 4, 1968 in Dr. Ivy's laboratory, 178 West Randolph Street, Chicago, Illinois.

Dr. Ivy was born in Farmington, Missouri, February 25, 1893. He received his Ph.D. degree in 1918 from the University of Chicago and his M.D. degree from Rush Medical College in 1922. He was Managing Editor of GASTROENTEROLOGY from 1942 to 1952 and President of the American Gastroenterological Association in 1940. He has received numerous honorary degrees and awards for his scientific, civic and military contributions in the past half century.

His career of research and teachings began in 1917 in Chicago, and he dominated the field of gastrointestinal physiology for a generation. His creativity may be partially assessed by his over 1500 publications and his training of 65 Ph.D. candidates.

At 75, Dr. Ivy continues a full schedule of research at the Ivy Cancer Research Foundation Laboratory.

EARLY YEARS

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Q: To verify some information, Dr. Ivy, you were born on February 25, 1893 in Farmington, Missouri, and you grew up in Cape Girardeau?

IVY: Yes. We moved from Farmington to Cape Girardeau, Missouri. My father was a teacher and so was my mother. He was Professor of Chemistry at the Teachers College in Cape Girardeau.

Q: What did your mother teach?

IVY: She was a high school teacher in Biology. She taught me the only physiology I knew prior to my Medical School courses.

Q: How did you decide to go into medicine, Dr. Ivy?

IVY: In order to make ends meet, my mother had to keep boarders. We had a large house. We would have from 8 to 10 of the college students and teachers as boarders. They'd get sick, and there was a doctor in Cape Girardeau who had practiced in the Civil War with the Federal Army. His name was Dr. Ryder, and he'd come to our house when the students became sick; and I would see them get well. I said: "That's what I want to be. I want to be a doctor and help sick people".

I remember that in 1899, when I was 6 years old, a friend of the family developed smallpox, against which I had been vaccinated. The patient was placed in a hearse and moved to the "pest house", located in a woods about a mile north of the city limits. I followed the hearse, keeping out of sight. I then climbed a tree near a window to see what was going on inside.

At the Teachers College in Cape Girardeau, I became interested in science and mathematics. I took a course in the psychology and philosophy of education and became interested in experimental psychology. My professor had received a Ph.D. degree with a major at Michigan and a minor at Wisconsin. He had a lot of new apparatus for experimental psychology, but illness prevented him from doing experimental work. When I completed the first course in psychology, I asked him what a person had to do in order to use his apparatus. He said if I would get 3 other students to work with me, he'd let us use the apparatus. He had a darkroom, which was relatively sound proof, for us to work in. We spent all of our spare time working in the laboratory and library.

My first research effort was in 1911, at the Teachers College. I completed several projects during the next two years. They were titled: "Arithmetical Ability Tests", "The Rate of Learning of Shorthand and Typewriting", "The Effect of Disciplined and undisciplined Play on the Post-Recess Conduct of Fifth Grade Students". In 1913, at the age of 20, I received the Bachelor of Arts and the Bachelor of Pedagogy degrees from the Teachers College.

The Professor of Psychology at the Teachers College wanted me to go to Oxford University in England and study the physiology of the nervous system with Sir Charles Sherington. I still leaned toward medicine and research in immunology. But, I had no money. My mother was a widow with two children of high school age to educate.

So, in 1913, after graduation, I obtained a position as Principal and coach of athletics in a high school in Clarksdale, Missouri. During one summer vacation, I worked as a civil engineer and during a second summer vacation as an electrical engineer.

By the summer of 1915, I had saved enough money to attend medical school for two years. I applied for admission to the University of Chicago and to Johns Hopkins. I was accepted by both schools, probably because I had received the senior medal in scholarship in 1913, when I graduated from the Teachers College.

I decided to attend the University of Chicago because I had been in Chicago before as a representative of the Y.M.C.A. My father and older brother had attended there and I felt that I could get a part-time job there.

Q: You entered the University of Chicago in the fall of 1915?

IVY: Yes, I received the B.S. degree from the University of Chicago in 1916. I received the Masters degree in Physiology in 1917, the Ph.D. in 1918, and the M.D. in 1922. I taught at the University of Chicago from March, 1917 to September, 1919. Then I got married and taught Physiology and Pharmacology at Loyola Medical School while I interned.

Q: So you were interning and teaching in the same year?

IVY: Yes, I'd teach 6 months and intern 6 months. When not on duty I was at work in my laboratory or with my family.

Q: You interned both at the Mercy and Augustana Hospitals in Chicago?

IVY: Yes, I was at Loyola Medical School from 1919 to 1922; however, in the summer of 1921 I taught physiology of the nervous system at the University of Chicago.

I shall never forget one amusing incident. As you know, physiology of the nervous system is not easy. Medical students consider that course to be the hardest course in physiology or even the hardest in in medical school. My students at Loyola had found that my courses in physiology of the blood, circulation, respiration, digestion, endocrinology and metabolism were tough. They had been told that my course on the nervous system was tougher. So, instead of taking my course at Loyola, 8 students decided to take the course the following summer at the University of Chicago, where they had been told the course was easier. The 8 students registered at the University of Chicago. When they showed up the first day, they were astounded when I walked in. They did not know that Chicago had employed me to give physiology of the nervous system there also. I continued to teach at Chicago until 1925.

Q: Then in 1925 you went to Northwestern?

IVY: Yes, we had a new physiology laboratory there, actually the largest and best equipped in the world. It had 20,000 square feet of space, not including 10,000 square feet of space for animals. We had from 20 to 50 graduate students yearly from 1928 to 1946.

Q: I understand that the lights seldom went off in the laboratory, that it was a 7 day a week affair there.

IVY: Well, I always went home on Saturday evenings to be with my family. Sunday mornings I'd go to church and to Sunday School with my wife and our boys, and occasionally I'd teach a class. The rest of Sunday, I frequently had to be in the laboratory to take care of the animals. At present, I go to my office and laboratory 7 days a week because I have to care for patients and animals.

Q: I recall reading that your wife would always pack a huge lunch. It struck me as very touching that a tremendous number of sandwiches always seemed to be left over for the graduate students in those days which were generally hard times through the country.

IVY: Yes; if any research student desired, he could sleep and prepare his meals in the laboratory.

Q: Tell me about your wife. What is Mrs. Ivy's first name?

IVY: Her name was Emma Anna Kohman. We were married in 1919. She has a Ph.D. degree in physiology from the University of Chicago. She was the first to demonstrate categorically the importance of protein in nutrition, in relation to the causation and prevention of what was called "starvation edema", or generalized anasarca due to inadequate amino acid intake.

Q: I see.

IVY: In World War I it was called "turnip disease" or "Rubenkrankheiten", because some people ate only turnips and roots. She was studying the nutritive value of carrots. She fed rats nothing but steamed carrots. She found that the rats, after a period of several weeks, would develop a generalized anasarca. Then, if she gave them 18% casein with the carrots, the rats would not develop edema; or, if they had edema, it would disappear.

Mrs. Ivy attended the University of Kansas. She took an advanced course in physiology, under a Miss Ida Hyde, who had obtained the Ph.D. degree under Dr. Howell at Johns Hopkins. On the recommendation of Professor Hyde, she was made an Assistant in Physiology at the University of Chicago. When needed, Mrs. Ivy has always helped me with my work. She can do any sort of work in the laboratory. She worked her way through college by teaching in high school.

Q: You were quite interested in athletics, I understand, and were spread out over a number of sports.

IVY: Yes, in college I played baseball, second base. I was in cross country track events. I ran 11 miles cross country in 55 minutes, which was a pretty good time in those days. In football, I played quarterback, and defensive end, because I liked to tackle. I weighed only 135 pounds, but size was no handicap. I could get tangled up in the legs of a big tackle before he got started. As a gymnast, I could do most of the stunts, but not very well. When the coach wanted his basketball team "roughed up", he'd call me in. I played tennis. I defeated the Missouri Valley champion, but not in an official competition. Our 5 boys have excelled in athletics and scholarship.

Q: You have 5 sons?

IVY: Five sons. One was an All-American tackle and a heavyweight wrestler also. Our third boy received the Big Ten Athletic Trophy for wrestling and football. Four of the boys were in the finals of the wrestling competition of the Big Ten in one year.

Q: You also wrestled, didn't you?

IVY: Yes. My weight was 135 pounds. I pinned the Big Ten Champion in an intramural contest at the University of Chicago. I did not qualify because I was a graduate student at the time.

Q: Tell me more about you and baseball.

IVY: I coached baseball in Mississippi, and several of my players became professionals in the Southern League. Several of my college team mates became professionals.

Q: You were also a boxer?

IVY: I could stand up to anyone in my weight. I defeated "all comers" in the Sixth Regiment of Missouri in 1909.

Q: Is that so, and you debated as well?

IVY: Yes, I liked to debate very much. I was an alternate on the debating team of the University of Chicago in 1916. I played the violin in the College Orchestra and the helicon bass in the College Band. At the University of Chicago I sang second tenor in the University choir and glee club. The income helped me study medicine.

Q: And you still managed to do rather well in school, despite those many outside activities.

IVY: Yes, I don't believe in wasting time. The first and most important thing for young people to learn is <u>not</u> to waste time. The way I prevented my medical students from wasting their time was to give them at least one written quiz every week, plus the possibility of a second one on the laboratory work. The students didn't have to cram for my courses. The weekly examination caused them to study consistently. I always returned the graded papers, and encouraged the students to complain if they thought a mistake in grading had been made.

Q: What are your 5 sons doing now?

IVY: The oldest is an internist and has a clinic at Elkhart, Indiana. The second has a clinic at Anchorage, Alaska. The third is a member of the Fronk Clinic in Honolulu. The fourth is on the staff of the Mayo Clinic. The fifth is Manager of Products and Promotion, G. D. Searle and Co., Chicago.

Q: How many grandchildren do you have?

IVY: We have 18 grandchildren, 11 girls and 7 boys.

INVESTIGATIVE WORK

INVESTIGATIVE WORK

Q: Dr. Ivy, which of your contributions to gastroenterology stands first in your mind.

IVY: I believe my most important contribution to gastroenterology has been to help produce, among others, over 270 medical scientists, most of whom are working and teaching in the United States, and more than 58 additional ones working abroad. I have taught physiology, and the physiology and anatomy of the signs and symptoms of disease to over 5000 medical students.

In the field of literary research in gastroenterology, our book on "Peptic Ulcer" has been important. I know of no book on the subject which has received more commedatory book reviews.

In the field of original research in gastroenterology, the preparation of a pouch of the entire stomach with or without the vagi cut, which was prepared from the study of "the phases of gastric secretion", made the subject clear to medical students and stimulated the performance of many researchers in the field of experimental surgery of the stomach and upper intestine. The transplantation of a part of the stomach, pancreas, and intestine subcutaneous established unequivocally a humoral mechanism for gastric and pancreatic secretion and demonstrated it was worth while to proceed to the isolation of the autacoids (hormones and chalones) involved in the regulation of the motor and secretory activity of the upper portion of the gastrointestinal tract. The study of the transplanted pouch disclosed the existence of a humoral agency (a) for acid secretion, (b) for fat inhibition (chalone) of gastric motility and secretion, and (c) for the excitation of hunger motility. It has been a great pleasure to have handed this "gold mine" over to Gregory and Grossman, my students, and to their colleagues, and to Uvnäs, Jorpes and Mutt, my friends.

The discovery of urogastrone, or of the existence of gastric secretory and motor inhibitory agents in the urine is an intersting contribution. However, the source and significance of these agents is obscure.

The discovery of cholecystokinin is my most striking discovery, because no one to my knowledge had suggested its existence, and, second, its discovery settled a controversy. At that time, some surgeons did not believe that the gallbladder contracted and evacuated and had a function.

As a result, some surgeons when operating in the upper abdomen performed a "Prophylactic cholecystectomy". For example, Dr. Sweet, Professor of Experimental Surgery at Cornell, claimed that "what enters the gallbladder never leaves it by the cystic duct". I studied the gallbladder from 75 patients, most of whom had had a "prophylactic cholecystectomy". The series showed cholesterosis of the gallbladder in all of its stages. This was before the day of cholecystography and color photography. Others took the position that the gallbladder was evacuated passively through the "milking action" of the intramural portion of the common bile duct.

I was interested in this controversy but actually was drawn into it by Dr. Carlson, who had been asked to present a paper on the physiology of the gallbladder in a symposium at the A.M.A. meetings in Washington, D. C., in June, 1927. Dr. Carlson had been interested in the liver, but not the gallbladder. However, I had heard him say that: "If God made the liver, the devil must have created the gallbladder, since it causes so much human misery".

Since Dr. Carlson knew that I had done some work on the biliary tract of the dog, he asked me to read his paper and make suggestions. I attended the symposium. Dr. George Burget, Professor of Physiology at the University of Oregon, who had received the Ph.D. degree at the University of Chicago, read a paper on the "milking action" of the duodenum on the common bile duct. We returned to Chicago by train together. While enroute, I told him I was going to try to discover the hormone which causes the gallbladder to contract and evacuate. I pointed out to him that even though none of the essayists had mentioned the possibility, all of the evidence presented could best be explained by assuming the existence of a hormone mechanism. When we parted Dr. Burget remarked: "Good luck with the hormone, Ivy".

When I arrived at my laboratory, I asked Dr. Eric Oldberg, who is now a prominent neurosurgeon in Chicago, if he wanted to help me discover the hormone which contracts and evacuates the gallbladder. He replied, "Yes". I said, "We shall start tomorrow; have a fasted cat ready". He said, "I have planned to leave for a 2 week vacation, and I have not had a vacation for 4 years". I said, "We shall do the first experiment 2 weeks from today. We shall by a simple method make a continuous record of the intra-gallbladder pressure, and then inject intravenously a vasodilatin-free secretin preparation, 'secretin A'. I think the gallbladder hormone is chemically closely related to secretin and will be in that preparation."

Two weeks later when we injected an aqueous solution of 'secretin A', the gallbladder of the cat contracted. The first step toward purification or concentration was to precipitate the hormone from an aqueous saline solution by adding acetone to a concentration of 85%. We then performed a cross-circulation between dogs with compatible (cross-matched) blood. When 0.1% hydrochloric acid was introduced into the duodenum of one dog, its gallbladder contracted in about 2 minutes, then after about 5 minutes the gallbladder of the other dog contracted. This was almost immediately confirmed by Professor Houssay of Argentina by transplantation of the gallbladder to the neck, and by Dr. Phillip Sandblom of Stockholm by blood transfusion. (Dr. Sandblom was recently retired as Chancellor of the University of Lund, Sweden.)

Beginning in 1922, I started to receive invitations to speak at meetings all over the United States. The surgeons and internists were much interested in learning about gastric and pancreatic secretion in relation to peptic ulcer. Dr. Frank Lahey and I were frequently on the same program. I would talk first, and what I said served as a background for his surgical procedures. The surgeons had been having trouble with post-gastroenterostomy marginal and jejunal ulcer. This served as an argument for the medical management of peptic ulcer, except in the presence of obstructive signs.

Dr. Frank Mann in 1917, in the U.S.A., was among the first to start an experimental study of the cause of this type of ulcer. In 1917, I found that clamps, if not used properly, would severely injure the delicate mucosa of the jejunum. The Mann-Williamson dog called attention to the importance of the acid, which in the basence of pancreatic juice and bile for neutralization, irritated the more sensitive jejunal mucosa. I and my colleagues used this preparation as a test in the dog of various therapeutic procedures.

The idea that gastric cancer originates in a chronic gastric ulcer was quite well recognized even as early as 1905. Between 1910 and 1920, Wilson and MacCarty of the Mayo Clinic had collected strongly presumptive evidence in support of this possibility. The importance of the possibility was generally opposed by internists. In 1918, I tried to produce gastric neoplasm in the mucosa of a pyloric pouch by making an acute ulcer and daily irritating it mechanically and chemically for one year. Even a benign adenoma was <u>not</u> produced. Later I fed daily methylcholanthrene, a very potent carcinogen to rabbits with a chronic gastric ulcer. Such treatment for from 8 to 18 months produced cystic and papillomatous lesions and epithelial inclusions in the ulcer scar, but not cancer. Still later in 1947, it was found that adenocarcinoma could be produced by implanting the carcinogen in the submucosa.

I lived through the advent of radical subtotal gastrectomy. The operation was introduced into Chicago primarily by the Strauss brothers and Richter. At first the operation met with much resistance, especially since more and more of the stomach was being removed.

In 1922, an experimental surgeon was quoted as saying that a dog would not tolerate total removal of the stomach. I performed a number of total gastrectomies on adult dogs, cats, monkeys, pigs, rats and calves to ascertain if any serious metabolic disturbance would result. The calves died of pneumonia. Otherwise the adult animals lived "indefinitely", if fed properly, but showed a predisposition to an iron deficiency anemia. Young puppies and monkeys when totally gastrectomized manifested stunting of skeletal growth, and homogenous osteoporosis. An occasional adult dog would develop osteoporosis.

About the same time, I decided to perform a subtotal gastric resection, removing from 66 to 75% of the fundus and all of the pylorus. It was found that after 6 months, most of the dogs secreted as much acid as they did before subtotal gastrectomy and that the gastric remnant had hypertrophied, so that it was approximately the same size as before the operation. However, in those dogs which did not bolt their food, the hypertrophy did not occur.

From around 1922 to 1935, Dr. Franklin Martin and his successor, Dr. Beesley, Secretary of the American College of Surgeons, would bring visiting foreign surgeons to visit my laboratory and observe operations, at the University of Chicago and later Northwestern. The value of experimental surgery on the alimentary tract was beginning to catch on.

On one occasion, I had taught my assistant, a medical student how to open the abdomen. Since I did not have hemostats, I taught him how to open the abdomen with a minimum of bleeding. One day I planned an operation for total gastrectomy at 2:00 P.M. I told the medical student to prepare the dog and open the abdomen and then call me. I went into my office to grade papers. I did not hear anyone enter the room where the dog was being opened. I was aroused when I heard a man with a British accent inquire of the medical student: "Doctor, how do you open the abdomen without loosing any blood"? The medical student replied: "Doctor, I know where the blood vessels are, and I cut where there are none". I rushed out to see what was going on, and Dr. Franklin Martin introduced me to Lord Dawson of Penn, Surgeon to the Royal Family of England.

Q: Can you recall any anecdotes about your research on peptic ulcer?

IVY: Your question recalls an experience I had at a symposium on peptic ulcer which occurred at a joint session of the sections on surgery and gastroenterology of the A.M.A. in June, 1920, at New Orleans. I had received the Ph.D. degree one year before, but had not received the M.D. degree. But, I had thoroughly studied the subject of peptic ulcer and had conducted research on it for over two years.

I prepared a thirty-minute paper with slides. As a non-member of the A.M.A., I did not know the rules for speakers and none had been sent to me. I had not seen the program until I arrived in New Orleans. The auditorium was filled with over 1,000 physicians, I was told. Physicians were standing along the walls.

I was first on the program and when I had presented about one-half of the paper, an alarm clock rang. The Chairman said: "Dr. Ivy, I am sorry, but your time is up". I replied, "Oh, I am just half finished". One of the speakers in the front row moved that I be given 15 more minutes; another speaker seconded the motion. After the symposium papers had been delivered, I, as the first speaker was invited to give a closing discussion. I declined. The remaining speakers gave their closing discussion. Then others were invited to give a discussion. Professor A. J. Ochsner of Chicago among others gave a discussion. He drew a tracing of the stomach on the blackboard, and then drew in a gastroenterostomy and said: "We make two holes in the stomach and when you stand or sit up the stomach empties easier by gravity". Several other discussors made statements which did not conform with recent physiological findings. The Chairman then invited me again to present a discussion. I arose and said: "Ladies and gentlemen, I have been very much interested in all the papers, and I have read publications by the speakers. However, some of the statements do not conform with present-day physiology, such as that the stomach empties by gravity. If that were so, our stomach would empty through our mouth if we stood on our heads. I advise everyone to read the recent issues of the 'American Journal of Physiology'." The audience was amused and applauded when I closed.

I turned in my paper to the Secretary for publication in the J.A.M.A. It was published, but not in toto.

It is obvious that I was a very naive young man from the hills and swamps of Southeast Missouri, who had been exposed medically only to the influence of Doctors Carlson and Luckhardt at the University of Chicago. Later I found that one prominent surgeon had been shocked by my discussion. This information came to me about one week later. Inquiry indicated that some of the Chicago members of the audience thought my statement was needed and that I had spoken in a jocular manner. I did not intend to be harsh. The following day I was cheered because Dr. A. J. Ochsner called me by phone and told me to come to see him when I wanted an interneship.

Q: Well, that's a marvelous story.

IVY: That was my introduction to the meetings of the A.M.A.

Q: Your book, "Peptic Ulcer", which was published in 1950, was a monumental work. Might I ask how long it took to actually write the book?

IVY: Its production was spread over 13 years. Duties assumed and incident to World War II, interrupted and delayed its completion.

Q: I am interested in hearing other anecdotes about your investigative work.

IVY: I have experienced a number of "flukes", or capricious and puzzling first-experiment results.

From 1910-1925, numerous surgeons ligated the superior thyroid artery on the theory that in hyperthyroidism excessive thyroid hormone entered the circulation via the superior thyroid veins. I decided to test this theory by ligating the carotid artery cephalward to the superior thyroid artery. This would shunt all the blood of one carotid through the thyroid gland. For this operation we selected dogs with a 3 or 4 times hypertrophy and trained them to sleep while their oxygen consumption was being measured. We also determined their resting temperature and heart rate. The first dog, about 6 hours after the operation, was panting and had a temperature of 106°F which rose to 108°F when clonic and toxic convulsions developed. The temperature rose to 110° to 112°F, and the dog died about 20 hours after the operation with a terminal temperature of 115°F. It was the picture of a "thyroid crisis" in the human. There was no infection (streptococcus) of the wound. Unfortunately we did not make a section of the brain. We repeated the operation on 10 additional dogs with a hypertrophied thyroid, but nothing happened. These observations were made two years after the introduction of iodized salt into Chicago. Prior to this 97% of all stray dogs had a goiter, and three years after, only 1 in a 100 dogs developed goiter.

Another "fluke" result occurred in relation to "intravenous sugar tolerance" and extirpation diabetes. As you will recall, splanchnic nerve impulses cause glycogenolysis in the liver. Dr. Gaza DeTakats and I determined the amount of glucose which when injected I.V. at a constant rate per hour would cause minimal glycosuria. Then we sectioned the splanchnic nerves bilaterally, and bilaterally excised the lumbar sympathetics. This denervation increased the glucose tolerance of all dogs from 1.8 to 4.0 times. Some dogs developed von Gierke's disease. We decided to extirpate the pancreas in the dog with the highest tolerance. We removed carefully all visible pancreas. We fed the dog the diet he had received before the denervation. The dog did not develop extirpation diabetes during a period of 6 months. This is analogous to the duck, which does not develop extirpation diabetes. So, Dr. DeTakats and I decided to explore the "adiabetic" dog for an abberant pancreas. We found none.

Q: I did not know that.

IVY: The chicken has an extirpation diabetes for about a week. Dr. Seitz and I found that the duck may develop a slight glycosuria the first day or two. I think the pituitary may be involved. It would be interesting to ascertain whether insulin is necessary for the use of glucose by muscle tissue in a duck. I could never obtain a grant-in-aid for extension of this subject or a student who was interested and qualified for such research. An anecdote which my graduate students like to tell occurred when Dr. Bussabarger was working on "entero-gastric regurgitation". One day we were sitting around the table in my laboratory eating lunch, and Dr. Bussabarger was complaining that there were not enough surgical instruments in the operating room. I commended that when we were at the University of Chicago we had to buy our own instruments, and besides, one didn't need very many instruments to do an operation on a dog. A few days later I was scheduled to do a unilateral splanchnectomy and lumbar sympathectomy with Dr. Bussabarger. He went around the laboratory inviting all the students to come in to the dog surgery and see what happens when 'the Chief' opens the sterilizer and finds out what instruments are going to be available to him to do the surgery. When I came into the operating room, about eight of the graduate students were present. When I opened the sterilizer there were 4 towel clips, a scissors, an aneurysm hook, and some black silk thread. I draped the dog with sterile towels, performed the operation amid a dead silence, and as I left the operating room, I asked, "What did you put the towel clips in for, Bussabarger?"

Q: Dr. Ivy, did you do any research on vagotomy in relation to peptic ulcer?

IVY: Yes. Our first work was a study of the effect of vagotomy on the stomach of rabbits. We found that bilateral section of the vagi in the rabbit led to the formation of chronic lesser curvature ulcers in the stomach. However, if the rabbit was fed a soft diet, the ulcers did not occur.

In my review of gastric secretion, published in Surgery in 1941, I reviewed the literature on the effect of vagotomy on the stomach. I pointed out that in view of our knowledge of the effect of vagotomy on the dog's stomach, a thorough trial of its value in the treatment of peptic ulcer was warranted.

I gave up my work on peptic ulcer after the publication of our book.

In 1959, I discontinued my research on the alimentary tract except for the chemistry of the hormone "gastrin". I confirmed Gregory and Tracy's observations. And, in 1966, I published an extensive review on the subject of "The Relation of Histamine to Gastric Secretion", in the Handbuch for Experimental Pharmacology (Springer-Verlag).

Q: I have observed that you have published extensively on cholesterol metabolism.

IVY: Yes, I have a series of 45 publications. In 1952, I became interested in the question of how the body maintains its cholesterol balance. I was interested because this is a very important question which had not been answered at that time. I was interested in this question also because it had a bearing on the future health of myself and Mrs. Ivy.

Q: What did you find out?

IVY: We studied the question in rats, chickens, dogs and human subjects. The average 150 pound person on a sterol free diet excretes approximately 400 mg. of digtonin precipitable sterol daily. So, on the basis of the depletion principal, the ingestion of 400 mg. of cholesterol daily should lead to storage of cholesterol unless hepatic synthesis is depressed, as it is in some animals (chicken), or cholic acid excretion is increased. Unfortunately, the existing evidence indicates that food cholesterol inhibits cholesterol synthesis in the liver of man very little or not at all. So, man is handicapped by having a mechanism in which absorbed food cholesterol does not reciprocally inhibit hepatic synthesis. This favors the body storage of any ingested cholesterol in excess of 400 mg. daily.

We found that excessive cholesterol is first stored in the liver, and then in the lining of blood vessels before it reaches a valve above normal in the blood plasma.

Q: How has your laboratory work continued in the last few years, Dr. Ivy?

IVY: I reached the compulsory age of 68 for retirement at the University of Illinois in 1961. The Board of Trustees retired me with the title of Distinguished Professor Emeritus of Physiology. The State Legislature passed a very complementary resolution unanimously recommending that I be provided space and a budget for research. I did not ask the University to act on the basis of this extraordinary resolution, since I did not believe it to be a desirable precedent.

Roosevelt University in 1961 offered me laboratory space with the title of Research Professor of Biochemistry. In 1966, the Ivy Cancer Research Foundation provided me with more commodious space.

In 1962, I discontinued all research other than that on the subject of the "body defense mechanisms against cancer". To me this is the most challanging problem in the entire field of natural science. It is also the most difficult.

My interest in cancer started in 1917 when 98% of stray dogs in Chicago had a goiter due to a dietary deficiency of iodine, which caused a "reactive hyperplasia" and which in turn underwent a malignant transformation in an occasional dog. I autopsied approximately 2000 goiterous dogs and found that almost 3% had developed a cancer of the thyroid with metastasis to the lungs. Others probably had malignant cells in their goiter, but I did not make an histological study because of lack of funds and because metastasis is the only true criterion of malignancy. I made a Locke's solution suspension of malignant cells from young metastases in the lungs, and, using a 15 gauge needle, injected over 20 million cells intravenously into dogs. These heterologous transplants did not grow. It appeared obvious that a resistance against the transformation of hyperplastic cells to malignant cells existed in goiterous animals. Also, a resistence against the transplantation of heterologous malignant thyroid cells existed in the lungs of dogs. This resistance could be either immunological, or of the nature of local chemical substances in the cells or released by injured cells which stimulate or inhibit growth or which cause the recently produced cell to undergo maturation. The existence of such mechanisms were known in 1917-18. At that time, a carcinolytic and an anticarcinolytic substance was found in the serum of non-cancer and cancer bearing patients, respectively. Willheim and Ivy have confirmed this.

In 1940, in view of the rapid rate of regeneration of the liver of rats, I planned to start a program to extract a growth promoting and a growth inhibiting substance from the liver. My appointment as Scientific Director of the Naval Medical Research Institute in 1942 interferred. My interest in cancer was renewed by my appointment as member and then Executive Director of the National Advisory Cancer Council (1944-1951).

As a result, I and my colleagues between 1945 and 1951 published 17 articles dealing with cancer. Some of the interesting titles were: Biology of Cancer; Thermal Irritation of the Stomach; Cancer Stimmulating and Inhibitory Substances in the Liver; Cancer, Reasons for Hope; Gastritis and Cancer Produced by Overheated Fats; Threshold of Skin Flare in Patients with Cancer. Between 1952 and 1961, 19 articles were published, the following being of interest: Lymphosarcoma and Cirrhosis of the Liver after Feeding Large Doses of Certified Food Dyes; Cancer Represents an Abnormal Repair of Injury; Carcinolytic Activity of Normal Human Serum for Cancer Cells; Decreased Resistance to Skin Cancer in Mice after feeding Certified Food Dyes.

Q: Dr. Ivy, you have been working on cancer research for some time now. Do you have any current hope that other investigators will engage in clinical trials of the "anticancer substance" which you extract from the blood plasma of horses?

IVY: I call the product which I have extracted since 1962 "Carcalon", meaning a "natural substance" which inhibits the cancerous process. It is non-toxic and non-allergic. I have evidence showing that it inhibits and occasionally produces a regression of the breast tumor in the C3H mouse. I have seen it reduce the size of a malignant tumor in some dogs. I find the substance in cattle plasma and cow's milk. I am studying goat's milk, now since it is reported to have stronger cancerolytic activity than any other plasma studied.

Answering your question, the "anticancer activity" of "Carcalon" in C3H mice has, during the past year (1968-1969), been confirmed by a cancer research specialist.

Regarding a clinical trial by other investigators, a clinical study by another cancer specialist is about to be initiated.

I have seen numerous patients respond favorably after other treatments have failed. But, like other treatments, to ascertain whether "Carcalon" will help, it must be given to the patient. In time, experience will increase and render percentages possible. In a series of approximately 500 case records, a committee of specialists accounted for the apparently complete remission in 2 cases as due to "natural causes". This is a frequency of 1 in 250 cases, whereas the best data available indicate that the frequency from "natural causes" is 1 in 50,000 in the human. The frequency of 1 in 250 is significantly less than 1 in 50,000. This would indicate that the "anticancer" substance was effective.

The presently used synthetic toxic cancer suppressives are physiologically irrational, because they are harmful or biologically nonspecific. Their use can only be justified by the occasional dramatic response which follows their use and by the hope that further research will finally yield a lethal or inhibitory substance specific for the cancer cell.

In the meantime, how shall we explain that some patients with a certain tumor respond to a worthwhile therapeutic extent, whereas others with the same type of tumor do not? Is this due to a difference in the biochemistry of the tumor cells or of the host? Furthermore, what are the natural causes of the "natural" or "spontaneous"remission. <u>The search for the cause or causes of the "natural and specific remission" can not be said to be more remote than the search for a synthetic specific chemical agent which only injures cancer cells.</u>

In 1951, I determined to remain loyal to the search for natural substances or mechanisms by which cancer cells are specifically destroyed. "Nature" has succeeded with this approach. In ascertaining how nature does something, we are not chasing a "will-of-the-wisp".

Some friends have charged me with being "stubborn"...I call it "tenacity". Without intending to place myself in the category of Louis Pasteur, I shall point out that he said: "Everything I have contributed, I owe to tenacity". After 18 years of effort, I feel that my tenacity has been fruitful. Much good and no harm has occurred. And, it is a great pleasure to observe the increase in our knowledge of the natural defense mechanisms against cancer in the body of animals. This has been and is a rational basis for the conviction and hope that a study of the natural regressions of cancer will lead to the "cure" of advanced or "hopeless" cancer.

Q: Were there any anecdotes connected with the "Big Trial"?

IVY: Yes, at least a dozen. One involved a crucial charge, namely that "Krebiozen" was "pure" or "practically pure" creatine monohydrate. The F.D.A. chemists said this was true. Dr. Durovic's chemists said that the product which he gave to the F.D.A. was 75% creatine-like substance and 25% "Krebiozen product". In the cross-examination of an F.D.A. chemist who had given the most clear-cut answers to questions, the following series of questions and answers occurred on the cross-examination by one of my attorneys:

Atty. S: Prof. C. did you weigh out some of Dr. Durovic's "Krebiozen Product"? If so, what color was it?

Prof. C: Yes. It was yellow.

Atty. S: Prof. C., did you weigh out some creatine mono-hydrate? If so, what color was it?

Prof. C: Yes. It was pure white.

Atty. S: Professor, I wonder where the yellow went?

This cross-examination was necessary to render it possible to tell the Jury, which knew nothing about organic chemistry and infrared spectroscopy, that "Krebiozen product" was obviously present in the sample given to the F.D.A.

There is another interesting and crucial anecdote. The F.D.A. placed on the stand several cancer specialists who testified at length. Their cross-examination proceeded in effect as follows:

Atty: Did you ever give "Krebiozen product" to an advanced cancer patient?

Spec: No, sir.

Atty: Doctor, there has been a lot of testimony about chemistry at this trial. Doctor, is there any chemical method by which you can tell whether or not an unknown substance is of value for some cancer patients?

Spec: No.

Atty: Do you have to give the unknown substance to a patient to find out?

Spec: Yes.

Another interesting point in the testimony was made when the F.D.A. attorneys were trying to prove that Dr. Durovic was "selling" his product. The F.D.A. brought in the relatives of 8 patients. On cross-examination these witnesses testified that the patient improved in all except one case.

Still another high point of the trial occurred when a surgeon testified who had removed a tumor from the breast of a patient. The F.D.A. attorneys were trying to impeach the surgeon because his estimate of the size of the tumor did not check with those of the pathologist. The explanation could not be made clearly to the jury. When the surgeon resumed the stand the following morning and the prosecutor tried further to embarass him, the surgeon reached under the desk and brought out a mannikin of the breast made with modelling clay and proceeded to show the jury exactly how he removed the tumor and that his measurements and those of the pathologist could be different.

After the trial was over, I tried to persuade the F.D.A. officials to have the President of the National Academy of Sciences appoint a Committee of Chemists who would study the data of the F.D.A. chemists and those of Dr. Durovic's to ascertain whether Dr. Durovic's product was "pure" or "practically pure" creatine monohydrate. The F.D.A. officials refused. They also refused when we made the same proposal to the Executive Offices of President Johnson. So, the request to show that the F.D.A. was wrong about this easily answered scientific question was refused.

My proposal to the American Cancer Society and the American Medical Association to settle the question of the value of the "Krebiozen product" was declined. I proposed that the matter be settled by a "clinical scientific" method. An arbitration committee would be established by appointing 2 specialists from the medical organizations and 2 from the "Krebiozen Research Foundation". A fifth member would be selected by the 4 appointees. Then the design of the test along with the criteria of efficacy or non-efficacy would be established. In Medical Clinical committees ground rules for the design and the criteria were to be set up after and not before a test. For example, the National Cancer Council committee took the position that the treatment was of no value unless it reduced the size of the tumor by 50%. No such requirement existed until the "Krebiozen product" was under trial. And, at the time, only a "fair" test was being asked for or proposed. If the product had reduced a tumor by 50% in size in only 25% of cases, there would be no need of a "test". Such a non-toxic substance would have had to be licensed for use. The method which I have proposed is the only scientific clinical way of promptly settling most medical controversies. This would shorten, I believe, the so-called laboratory-scientific lag. The most recent example is cited in the quote from Alexander Fleming; namely, "Penicillin sat on the laboratory shelf for 12 years while I was being called a quack".

I should add that some 5 different investigators in addition to me have now reported finding "anticancer" or "antigrowth" substances in blood plasma, urine, or body tissues.

My health is good now. If it remains good, I shall continue to work on the problem of the "advanced" or "hopeless" cancer patient. There are three aspects of a physician's service to a patient; one is science or knowledge, a second is skill in the application of knowledge and experience, the other is sympathy and hope. The latter is sometimes all that we can offer the patient. Some have said, "We should not give false hope". This is sophistry. I do not believe in lying to patients. A good physician does not have to lie to give the patient hope. And, 95% of the patients I have seen have lived on "false hope", medically speaking, to the extent of the $5,000 to $50,000 they have paid for prior treatment. When you stop and think it becomes evident that from day to day we all live on "false hope" much of our life. The research continues on the basis of "hope", and in many instances his efforts have found "pay dirt" in not more than 10% of instances. The patient is not charged for the experimental therapy, and has nothing to loose.

Philosophically, I believe that one is a loser unless one derives compensation simply from searching for the truth. You may not make a discovery, but you can not be deprived of the joy of trying.

I have always enjoyed my work. I am enjoying my work now. I should not say "enjoy", that isn't the word, because too many of my patients get a hold of my heart and squeeze it too hard. But, I receive due gratification from my efforts.

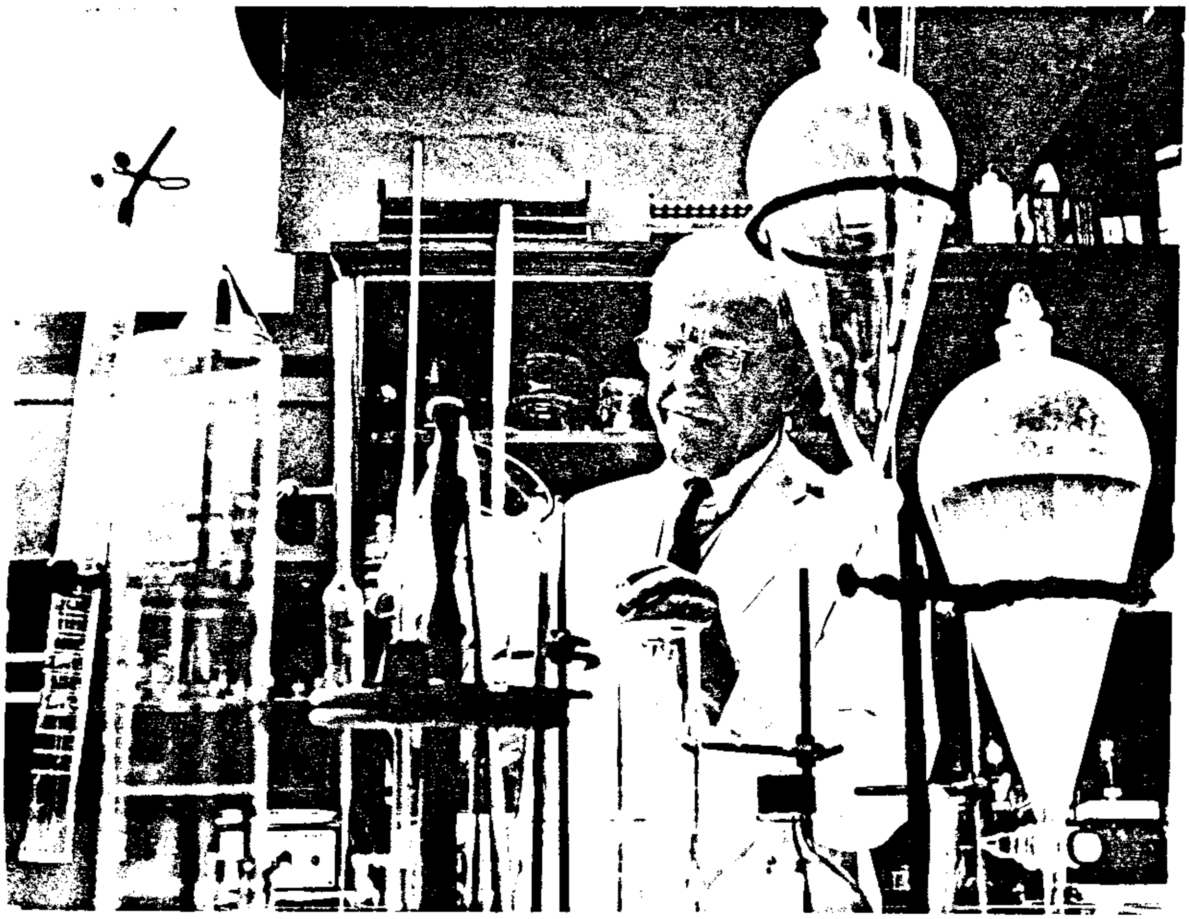
Q: I can certainly see that. Do you attend the International Congresses of Gastroenterology?

IVY: I have attended several, including the last two. I attended the last International Congress in Prague in 1968. I attended the last Pan-American Congress in Lima, Peru. Former students were the Secretary-General of both.

Q: I understand that you received a standing ovation at the last Congress in Prague.

IVY: Yes. I was listed to give a paper and when I arose and walked to the podium, Dr. R. A. Gregory, who received the Ph.D. degree under my instruction and who was Chairman, initiated the standing ovation. I appreciated it very much.

GASTROENTEROLOGY IN CHICAGO



DR. IVY IN HIS LABORATORY ON RANDOLPH STREET IN CHICAGO

GASTROENTEROLOGY IN CHICAGO

Q: I am interested in Chicago as the center of American gastroenterology in the first half of this century. In tracing the career of any current gastrointestinal physiologist, sooner or later his past intercepts with Chicago. Did gastrointestinal research in Chicago begin with A. J. Carlson?

IVY: Yes. Nationally, it began with Cannon of Boston in 1898 and his work movements of the esophagus. In 1910 Cannon changed to the adrenal gland. Carlson of Chicago started in 1904 with the invertebrate heart, and in 1912 switched to gastric motility and secretion, and extended Cannon's work on hunger. Carlson produced more Doctors and Masters degree graduates in physiology than anyone during his prime. Then, in 1917, I followed Carlson and have helped produce over 205 Masters and over 65 Doctors in Physiology and Pharmacology. More than 105 are Professors in medical schools.

Q: You trained under Carlson. Would you tell me about him?

IVY: I worked in Dr. Carlson's laboratories for a total of 5 years. He was the outstanding contemporary critic in the field of physiology and medicine. He recognized the crucial point in a research presentation or discussion, and indicated the relation of "de evidence" to the crucial point. He was an outstanding teacher for graduate students. There has been no better. I can tell you more about Dr. Carlson by telling you anecdotes.

As a debator in college, I learned to ascertain and emphasize the crucial issue required to clear up confusion. As a student of Carlson, this approach to a research problem was cultivated and stimulated. That's why I made a pouch of the entire stomach with and without the vagi cut in order to study "the phases of gastric secretion". Then, to settle the "gastrin controversy", and also the "secretin controversy", I transplanted a part of these organs under the skin and watched them function with a new blood supply and no extrinsic nerve supply. In the Spring of 1923, I told Dr. Carlson that I was going to transplant a small gastric pouch under the skin of a female dog. He replied: "Dot ist impossible". I rejoined: "Dr. Carlson, please come to my laboratory. I will show you that it has already been done and that the pouch secretes after a meal. Then, I would like for you to operate the dog and see for yourself that all visceral extrinsic nerves and blood vessels to the pouch have been cut."

Of course, that demonstration pleased Dr. Carlson a great deal. Another thing that pleased Dr. Carlson was to have a student argue with him. However, he expected the student to be prepared and to be able to think logically. I remember the first meeting I ever had with Dr. Carlson in his office. I disagreed with a statement he had made in a lecture about a function of the vagi. It was about "Vagotonia". So, I went to his office one morning about seven o'clock. He usually arrived before seven o'clock. I told him that I was a student in his class and would like to talk to him about a question that had come up in his course in physiology. He said, "Come in". I told him what the question was. He answered it; and I said, "I don't believe your statement is correct for these reasons"; and he said, "Vell, do some research on it". It never dawned on me, until I had actually told him that I disagreed with him that, here I was, just a freshman medical student, disagreeing with a renowned professor of physiology. I wondered why he didn't dismiss me from his office. He was tolerant of freshman college students, but not of medical students. He expected medical students, physicians and graduate students to be prepared, and, hence, to ask rational questions and to think logically and analytically.

For example, the first contact that I had with Dr. Carlson in the laboratory was as a freshman medical student. He was in charge of the laboratory. We were studying the circulation and secretion of the submaxillary gland, and I was the surgeon on the dog that day. We were going to study the effect of stimulating the nerves going to the gland on the blood flow. We had to cannulate the salivary duct and to cannulate the venous blood supply and isolate the extrinsic nerves of the gland. Dr. Carlson told us how to do this, and he said, "You cut through the skin with the knife, and then you come to some tough tissue. You go through that tough tissue with a probe. Don't use a knife! If you do you'll cut a vein, and the field will become bloody, and you'll spoil your dog and the experiment." I was the surgeon. I'd gone through the skin, and there was that layer of tough tissue, and I thought it was not good surgery to take the probe and pick through that layer of tough fascia. So, I picked up the knife. My fellow students who were in the group with me said, "Ivy, don't do that, you'll get into trouble". I said, "What's a knife for?" Then I cut a vein. They ceased talking, because they saw Dr. Carlson coming. Dr. Carlson stopped by my side and shaking his finger in my face, said: "Didn't I tell you that you would cut a vein if you used a knife?" I looked at him and I said, "Yes, sir, Dr. Carlson. I proved what you said to be true." He turned around and walked off. I'll never forget that confrontation. My fellow students were astounded. So was I.

Q: You worked with him for quite a number of years.

IVY: A total of 5 years. I went to Chicago as a student in September, 1915. I took physiology of the blood circulation and respiration in the Spring of 1916. He lectured to us on the heart. In the Fall of 1916 I studied gastrointestinal physiology with Doctors Carlson and Luckhardt. In the laboratory, I had a discussion with Dr. Carlson regarding the effect of water on gastric emptying and the onset of hunger. He told me that I should do research on that subject. I started research on the subject in the Winter of 1917. The same quarter I had a course on the physiology of the nervous system under Dr. Carlson. Dr. Carlson asked me to remove aseptically the motor area from the brain of a dog, and when the dog recovered to demonstrate the dog to the class. I had never performed an aseptic operation, but I had seen several. So, I operated, and the dog recovered without an infection. Dr. Carlson asked me to demonstrate the dog, which was now my "pet", to 4 different classes. It was a classical "Goltz Dog".

After the mid-term examination, Dr. Carlson offered me a scholarship. I said: "Dr. Carlson, I'm very much interested in physiology, but I really came to medical school to do research on immunology and cancer. I am very interested in immunity, even though I have become interested in research through experimental psychology". I said, "Dr. Carlson I want to be fair with you, because I'm doing research work in the Department of Pathology on the Leviditti stains with Dr. Hirsch right now, and I should like to try to settle the controversy on syphilitic heart disease". I told him that I was doing advanced work in pathology and performing some autopsies at the Cook County Hospital. He replied: "Vell, dot ist physiology too". Dr. Carlson then asked: "Vere do you get money to pay your expenses?" I said, "I have to make my own way. My mother is a widow." Dr. Carlson then said: "If you need any money, der ist a scholarship waiting for you over at the Graduate Dean's office. You may go over there and pick it up."

In the Spring of 1917, I took Dr. Carlson's advanced course in endocrinology. Then he went to war in the Nutrition Corps of the U.S. Army. He placed me in charge of teaching his course in endocrinology. It was the first systematic course with lectures and laboratory manual to be offered by a University or Medical school on the subject of endocrinology. Dr. Carlson was a member of the Hoover Commission to study nutritional diseases in the War-stricken Countries after World War I. When he returned in the Summer of 1919, I had received the Ph.D. degree in 1918, and in 1919, I had been appointed Associate Professor of Physiology and Pharmacology at Loyola Medical School. Dr. Carlson returned me to the University of Chicago in 1922 as Associate Professor of Physiology with a good salary and a research assistant. In those days, one had to buy his own instruments and laboratory gowns. I had to do my own diener work. However, medical students were always pleased to help, because they assisted me with my aseptic surgery. In 1925 I moved from the University of Chicago to Northwestern University Medical School as Professor and Head of the Division of Physiology, Pharmacology, Therapeutic's and Materia Medica.

Q: I see. Can you tell me any more about Carlson?

IVY: I can best tell you some more anecdotes, since that is the best way to describe the man. Dr. Carlson was a legend even as early as 1915 in the American Physiological Society, because he was always doing something of a type that was difficult to forget. For example, he was chairing a meeting on the adrenals at the Annual meeting of the Physiological Society. Biedel, who was the Endocrinologist at the University of Berlin had presented some of his work on the adrenals at the American Physiological Society. At that time a terrific controversy was in progress between Cannon of Harvard and Stewart of Western Reserve. The controversy involved the function of epinephrine. Biedel had spoken once in defense of Cannon. Then Hoskins of Harvard spoke in defense of Cannon. Then Hoskins of Harvard spoke in defense of Cannon. Then Biedel arose again and started to speak. A few minutes later Dr. Carlson said: "Biedel sit down, you have already said dot once. And, dot ist enough." This was said with a Swedish accent and concluded the controversy with uproaring laughter.

Sometimes he would make the speaker mad by his criticism. Later, he would ask me whether he had done right. For example, in 1926, Dr. Carlson and I went to the International Congress of Physiology in Stockholm. Dr. Varnoff of Paris was there. Dr. Varnoff had been doing testicular transplants and had presented his observations. He presented photographs which were very subject to suspicion. Dr. Carlson subjected Dr. Varnoff's evidence to severe but witty criticism. Later as I was walking out of the building with Dr. Carlson, he said to me: "Ivy, did I do the right think by yumping on Varnoff the way I did?" I said: "Well, Dr. Carlson, I think somebody had to do it, and you were the only man who had the wit and courage to do it. Your justification was assured when the chairman of the French delegation to the Congress stood up at the meeting and unnecessarily apologized for the presence of Dr. Varnoff at the meeting." This is why Dr. Carlson had frequently been said to have been the most outstanding and witty critic in the field of research and clinical medicine during his lifetime.

Here's an interesting story indicating that the criticism of Dr. Carlson on occasion might have been destructive in nature. On one occasion Dr. E. L. Scott, in 1912, made an extract of the pancreas in the laboratory at the University of Chicago and injected into diabetic dogs, causing their blood sugar to decrease. He presented his observations to the seminar at the University. Dr. Carlson suggested that the decrease in blood sugar might have been due to a toxic effect of the extract. Scott became irritated and moved to Columbia University and never worked on that problem again. Ten years later Banting, Best and Collip worked on the problem and produced a better product than Scott, which, of course, was "insulin".

Q: Among Chicago gastroenterologists, Frank Smithies comes to mind. He was President of the AGA in 1929. I have read of his accomplishments but don't feel I know what he was like as a person.

IVY: All the negative criticism of Dr. Smithies consisted of harsh remarks made on a background of jealousy. Frank Smithies was on the staff of the Mayo Clinic before he came to Chicago. He was one of the first men on the Mayo Staff to leave there and come to Chicago, so that created some jealousy in the first place. In the second place, he started using the Lyon drainage of the gall bladder which had split the GI profession into two camps. Some took the position that if you used it you were a "quack". I looked into it myself and felt that if intelligently used, it was at that time as good a diagnostic method for some cases as one could employ. This was before the days of cholecystography and cholecystokinin.

Dr. Smithies was an alert person and would tentatively accept, test and develop new ideas. He was also in the midst of the controversy on the medical and surgical treatment of gastric and duodenal ulcer. You will recall that the gastroenterostomy was first introduced into the medical profession solely as a treatment for obstructive conditions of the stomach and duodenum. Moynihan was the first, or among the first, who said the profession should treat duodenal ulcer with gastroenterostomy.

At that time Dr. Smithies had a very large practice and he used the most modern diagnostic techniques. I know because I interned where he had been head of medicine, at Augustana Hospital, and where Professor A. J. Ochsner, the celebrated surgeon, was the chief personality. Dr. Smithies and he frequently disagreed. So, they kept apart. The first thing that they told me when I went there to intern and to serve as a resident and Chief of the Diagnostic Laboratory was that I should not argue with the "Professor", because I'd have trouble; but they told me that I could argue with Dr. Smithies. I found that he had a relatively very large clinical material; next to Sippy he had the most gastrointestinal patients in Chicago. This created some jealousy. I know because I was an externe on the Sippy Service for 6 months. I had gained experience with some of Dr. Smithies' patients for 4 months.

Because the amebic dysentery epidemic occurred in Chicago in 1932, Dr. Smithies had presented a paper to the Chicago Society of Internal Medicine on the subject. He reported on a relatively large number of such patients. It was so large that great skepticism was manifested by the members. In private conversations, he was referred to as a liar. It was not long after this condemnation of Dr. Smithies that Dr. Williamson, Professor of Medicine at the University of Illinois, working in the out-patient dispensary reported diagnosing even more cases of amebic dysentary than Smithies. When I was an interne at Augustana in 1922, cases of amebic dysentery were common. Most every patient received a "warm" stool examination. Dr. Smithies had numerous patients with tropical diseases. Patients with chronic malaria were common. He had many Spanish speaking patients. He visited Mexico and Latin America frequently. He spoke Spanish and was an excellent speaker and debator. He was considered to be an excellent diagnostician and used the laboratory frequently for his time.

Furthermore, I came to Chicago in 1915, and as a freshman medical student I started attending most all the medical society meetings in Chicago, especially if the meeting involved a controversial subject. This was the best way to ascertain what was happening on the frontiers of medicine. Most every Saturday morning I attended Dr. Sippy's Clinic or the Clinics at Cook County Hospital. I never found a sound basis for the criticism of Dr. Smithies, or of Dr. Sippy.

After 1930, Dr. Smithies spent more time with the GI Section of the A.M.A. and the American College of Physicians, of which he was a founder and its first General Secretary.

As a result of attending the Cook County Clinics and various medical meetings, I was permitted in 1917 to perform my first clinical research at Cook County Hospital. It involved the study of the motility of the stomach and sensory changes before and after a chordotomy on a patient with the weekly occurrence of a gastric crisis in tertiary syphilis.

Q: Did you know Dr. Sippy and Dr. R. C. Brown?

IVY: Yes, I knew both. Dr. Brown was considered by students and most physicians to be second only to Dr. Sippy as a diagnostician and therapist.

He was a very careful diagnostician. He was quite formal and reserved. One learned best from him by asking questions. He was always patient with me.

Dr. Sippy was not only a shrewd diagnostician and therapist, he was also an outstanding teacher for medical students. He was a showman and a dramatist. His patients and students worshipped him; "He couldn't make a mistake". In the big amphitheater where his "Big Clinic" was held on Saturday morning, there were two or three chairs which he used. He frequently stood on one of those 24-inch high chairs and lectured. Sometimes he had 2 chairs and would change from one to the other. On one occasion the chair on which he stood started to collapse, and just at the right time he stepped over to the other chair without missing a word.

Patients filled the semicircular bench in fron of him listening to very word he said. One Saturday he was dealing with a controversial topic. When he made his concluding remark, he pointed to the patient sitting at one end of the semi-circle of patients, and asked: "Isn't that so?" The patient replied, "Yes". Every patient except the last one in the row replied, "Yes". This last patient replied, "Yes, Dr. Sippy; but why do all the other specialists so 'No'?"

When I attended Dr. Sippy's Clinics, he was in a controversy with Dr. Carlson regarding the genesis of pain in peptic ulcer. Dr. Sippy obviously enjoyed this argument with Dr. Carlson. Sippy, like many "City physicians" in the U.S.A. described "ulcer pain" as continuous and burning in type. Dr. Carlson had made some gastric balloon motility studies on a few patients and found the pain to be intermittent in type and would occur with tonic hunger-like contractions of the stomach. Most physicians sided with Sippy, a few with Carlson. However, the European literature spoke of ulcer pain as being like "hunger pain". At the height of the controversy, one of Dr. Sippy's internes, at 2:00 A.M., was called to take care of an ulcer patient. He grabbed his Ewald tube and bulb, and while running through the hall, he bumped into another intern who said: "Nesbit, where are you going with that garden hose?" And Nesbit replied: "To take care of a burning distress." (In this period of from 1915 to 1920, some of the clinical teachers "poked fun" at the teachers in the pre-clinical sciences at the University of Chicago.)

This controvery regarding the genesis of pain in peptic ulcer led to my second clinical investigation. I desired to ascertain the cause of the controversy. With the permission of Dr. Sippy and Brown, I studied their patients, both ward and private patients. First, I found that most of their patients had never been deprived of food long enough to know what "hunger pain" is like. Second, there were more patients with duodenal than gastric ulcer. Third, intermittent pain was more common with gastric ulcer, which appeared to be more common in Europe. Fourth, burning distress was more characteristic of duodenal or outlet ulcer, with gastric retention of highly acid gastric juice. Fifth, continuous pressure-like pain was more characteristic of serosal involvement and was slow to respond to neutralization. Sixth, when distress was not relieved by complete neutralization, muscle "spasm" or serosal involvement were most likely involved.

Dr. Sippy did not like to be called a "specialist". He said: "I am an internist". This may be the reason why he did not regularly attend the annual meetings of the A.G.A. Dr. Sippy probably produced more clinical gastroenterologists than anyone, except Dr. Bockus perhaps.

Q: Dr. Brown became President of the Association in 1936.

IVY: Yes, the honor was well deserved.

Q: One last thing about Chicago. Would you tell me about the "American College of Dog Surgeons", or the "Collegium Chirurgium Canium Americum", which I have heard you founded.

IVY: It was founded by Dr. Carl Dragstedt, the pharmacologist at Northwestern. I was more of a "Godfather". The organization was a kindly burlesque on the American College of Surgeons. Each year in the Spring "The College" met and initiated qualified persons who had applied and written a "Thesis". The persons were graduate students, or human surgeons who had made a surgical contribution by operating on dogs. The annual meeting was a very interesting and entertaining affair. Dr. Boyle, where did you learn about this organization?

Q: I saw a diploma in Morton Grossman's office.

IVY: I have here a bound volume of some of the theses written by graduate students at the University of Illinois.

Q: May I quote from the Table of Contents some of the subjects of the theses?

IVY: Of course.

Q: "The Relationship of an Elephant to Man and Women", "The Study of Hypertensors or Hemogremlins, Their Activity, Behavior, and Other Such Stuff and Nonsense". The last is by Lionel Bernstein. There are many famous names here: James Roth, Rhoda Grant, Martin Kalser, Armand Littman, John Gray, Fred Grodins, Ralph Sonnenshein and William Bachrach.

IVY: Dr. Carlson was initiated and given a diploma. They put a dog collar on him, and led him into the room by a chain. He was nonplussed. I had never seen him nonplussed before, nor since. He didn't know whether to take his initiation as a joke or to take it seriously. He was speechless.

Q: That's marvelous. I imagine this is the one existing collection of the theses.

IVY: Yes, I believe it is the only bound volume which exists.

Q: What is the Greek lettering on the book plate?

IVY: That is my book plate. Translated it reads: "Prove all things, and hold fast to that which is true".

Q: That's very nice.

IVY: That's from the Bible, St. Paul. The book plate shows the "Organs of Progress". The heart stands for compassion, the stomach for courage, the labyrinth for balance, the brain for intelligence, the eye for insight, the book for knowledge and the muscle for work.

THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION:

PERSONAL REMINISCENCES

THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION:

PERSONAL REMINISCENSES

Q: How did you get started in the American Gastroenterological Association, Dr. Ivy? Do you remember who put you up?

IVY: In 1923, I had prepared my first report on "the phases of gastric secretion". I did not have money enough to go to the meeting. I asked Dr. Carlson to read my paper. Dr. Carlson also read my paper at the Section on Gastroenterology of the A.M.A. I presume Dr. Carlson nominated me for membership, since I now had the M.D. degree.

Q: Dr. Ivy, you are largely responsible for founding the A.G.A.'s present official journal, "Gastroenterology". How did that come about?

IVY: I gave a brief account before. When I became President of the Association in 1940-41, the journal to which the Association lent its prestige, namely, the American Journal of Digestive Diseases, was being criticized by the members, who believed they did not have sufficient editorial control over the articles and the advertising published. In addition, some members believed that the Association should be receiving some financial return. I had published (maybe buried) numerous articles in this Journal, including some very important ones on bile secretion and the effect of aspirin and cinochophen on the stomach and duodenum.

I conversed with the editor and owner of this Journal concerning the possibility of the A.G.A., assuming the editorial control of the article and the advertising. I found the door closed to any type of cooperation. I reported this to the Trustees of the Association.

I, and other members, felt that the Association should have a journal of its own. There were plenty of papers in the GI field to warrant a journal in that field. I pointed out the well known fact that patients complain of the signs and symptoms of gastrointestinal disturbances more frequently than in the disease of any other functional system of the body. For example, symptoms referable to the alimentary tract may occur in heart, mental and neurological, genitourinary, endocrinological, pulmonary, and infectious disease. I indicated that if from one-half to two-thirds of the papers were clinical and appealing to practitioners of medicine, there would be no difficulty making such a journal profitable. I suggested that we could obtain a publisher who would agree to permit the Association to see and approve for publication all advertisements. Dr. A. Aaron, the Treasurer of the Association, had agreed to serve in that capacity.

At that time, I had gained experience with the publications of the American Physiological Society. As a result of that experience, I knew the financial aspects of the management of journals quite well. I had set up a Board of Publication Trustees when their Journal was financially weak. When I left the management the Society had a publication fund of $350,000. I pointed out to the Board of Governors of the A.G.A. that they had wanted to set up a scholarship fund. At every business meeting since 1927 someone spoke to the members present about getting some wealthy benefactor to give them some money to establish a research fellowship, or to do other things of that sort which most other medical associations were doing at that time. I indicated that I was sure that if they accepted advertising of a quality that the AMA accepted and a committee passed on these advertisements, we would be able to make a profit.

Furthermore, in order to break even on the publication of the journal, we only needed 1000 subscriptions. I believed we could start out with 1000 or more subscribers, if we could persuade a good publisher who was willing to put some capital into the project. We could solicit the members of the Association, of the GI section of the AMA, the libraries, and all the physicians in the Index Medicus who had published an article on a gastroenterological subject. I had written to some 60 friends to ascertain if they could send an article for the first volume. The response was greater than anticipated. I did this to show the Board that we would have no trouble getting papers. Another argument against producing a journal was that a new journal could not be started when a war was in progress. There was no evidence to support this suggestion.

I was given permission to investigate further and to negotiate a contract tentatively for further discussion.

I had done some business with the publishing firm of Williams and Wilkins of Baltimore when I was Chairman of the Board of publication trustees of the American Physiological Society. I also had discussed the project with Mr. C. C. Thomas, the publisher, at Springfield, Illinois. I knew both to be reliable and to be firms with principles.

Q: I see.

IVY: After meeting with Mr. Gill of Williams and Wilkins and with Mr. Thomas, I asked them to send me a tentative contract proposal. They did, but the tentative Thomas contract was not as financially attractive as that of Mr. Gill. Mr. Gill's contract met all requirements and proposed that the Association be a partner with Williams and Wilkins Co. However, the Board, being very cautious and the Association being without money, expressed fear that the journal would not make a profit and the loss would have to be shared with Williams and Wilkins Co. But, I strongly felt that the Association should have a Journal and was backed up by Dr. Aaron and Dr. Sara Jordon.. So, I proposed a very unusual contract plan to Williams and Wilkins providing that Williams and Wilkins would assume all losses. Then, in order to give the Association an opportunity to assume no risks but to own their journal wholly, a stipulation was added providing that at the end of five years the Association could purchase the Williams and Wilkins share by paying Williams and Wilkins the sum of all profits the Association had received during the first five years. The Association made a profit the first year and in each of the first 5 years. However, the partnership had gone so smoothly during the first 5 years, the Association voted to continue it.

During the period I was negotiating with Mr. Gill, I frequently traveled to Washington, D. C. to attend committee meetings. This decreased my personal expense, since I stopped off going to or from Washington. Also, most of the first volume of Gastroenterology was put together and to bed when I was scientific Director of the Naval Medical Research Institute. At this time I was organizing a research staff and starting research programs at the Institute. The correspondence went to my office in Chicago and was forwarded to me at Bethesda. I answered in longhand and forwarded it to Chicago where it was typed. Dr. Aaron handled the advertising with skill, and I was always prompt in its return to the publisher.

Q: You made a profit the very first year, I understand.

IVY: Yes, I was certain we would.

Q: No one else was quite so sure.

IVY: Dr. Aaron and Dr. Jordan were willing to assume a risk. The other members of the Board were very cautious. This caution resulted in a perfect contract. Mr. Gill was as certain as I that we would make profit the first year, and he had been in the publishing business for a long time. The journal has been more successful than I imagined at the time, and I have always had a very good imagination. A research man has to have a good imagination.

Q: Dr. Ivy, I wonder if there is anything else that stands out about your Presidency in 1940-41?

IVY: As President, practically all of my time was spent in getting the Journal started.

Q: I have a list of the founders here. Many of these probably had died before you came into the Association.

IVY: Dr. Aaron was always active in the management of the Association. Dr. Friedenwald was active. Allen Jones was active intermittently; he was very highly thought of. Doctors Einhorn and Friedenwald discussed almost every paper that was presented. It was a very stimulating type of discussion. They were very well read.

Q: Could you contrast the early meetings with the current meetings, Dr. Ivy? An early meeting which you might recall for instance in the 20's?

IVY: Well, there is a great contrast. I attended the meetings of other specialty groups, and the GI group was the most stimulating. It never became boresome. That was because of the discussion and arguments. The papers were principally clinical, where there is more room for differences of opinion. More discussion was allowed then than now.

Q: Did the discussions differ from other specialty organizations of the 20's? For instance, were the discussions more meaningful?

IVY: I believe so. That's why they were more interesting. At times the discussions about the medical management of peptic ulcer were heated. They discussed hourly neutralization; continuous neutralization by stomach tube, and the starvation treatment. Most all were against gastroenterostomy for duodenal ulcer. There was only one indication, and that was obstruction. Duodenal drainage aroused much discussion.

Q: Here is a list of some of the A.G.A. members active in the 1920's and 1930's, some of whom we've already talked about.

IVY: I shall offer only my impressions. I shall try to be accurate, but I knew some of the persons better than others.

Walter Cannon was a fine man and an imaginative investigator. He was the first basic scientist elected as President of the Association. Following Beaumont, Cannon did the most outstanding work in gastroenterology in the U.S.A. I received three postal cards from Dr. Cannon, each of which contained a congratulatory message, one related to the "Phases of Gastric Secretion", one to the transplantation of the stomach pouch and the other to cholecystokinin.

Then, Carlson followed Cannon and became very prominent.

Dr. Bastedo was a pharmacologist; he did not attend the meetings regularly. I saw him only once. He was a polished and friendly person and a good teacher. Andresen was a loyal worker for gastroenterology and the Association, a man of high ideals, very serious, but friendly. He was a good teacher and well-read. Irwin Abel was a prominent surgeon and southern gentleman from Louisville, Kentucky. He impressed one as being a clinician with sound judgement. He was frequent and well received lecturer at state medical meetings all over the country. Abe Aaron, of course, ran the society for many years. He assumed all responsibilities, and was prompt. When there was friction, he was the one to use the oil effectively.

Comfort was a good scientist and clinician. He and I frequently discussed problems concerning the pancreas.

George Eusterman was highly respected and well-liked. He was a good diplomat and very loyal to the Association and gastroenterology.

Bockus is a fine man and is highly respected. He is an excellent clinician. He is a good speaker and is well-read. He has held and defended strong opinions. He is an able critic. I sent him a number of my students for clinical training in gastroenterology.

Boles has been very loyal to the Association, and regular in attendance. He is a polished speaker, a scholarly type. He has been very active in gastroenterology and the Association. He has been a leader in the Association since he became a member.

Frank Smithies: I spoke about him earlier.

Franklin White. He was a polished gentleman, a good clinician, and well liked by every one.

Vincent Lyon. He was loyal to the Association and was an enthusiastic person who liked to perform research. He most always provoked an argument every place he spoke. He liked to discuss his work, and I profited from the several discussions I had with him.

Chester Jones was a good clinician, a careful investigator and very loyal to gastroenterology. He was an excellent speaker and had a diplomatic personality. He is one of the group of prestigious gastroenterologists who contributed to the recognition of gastroenterology as a sub-specialty under the Board of Internal Medicine.

George Piersol was regular in attendence. He seemed to enjoy the meetings. He occasionally discussed a paper, always interestingly. He greeted every one cordially. He was known better in the field of physical medicine. He was one of the founders of the Council on Physical Medicine and Rehabilitation of the A.M.A. I happen to know this because I was a member of the Baruch Committee to up-grade teaching and research on the subject, and hence its status. I received a Distinguished Service Award from the College of Physical Medicine and Rehabilitation. We discussed only physical medicine when we met. I happened to be a Consultant on Physical Medicine in the Veterans Administration Hospitals immediately after World War II, and lectured and inspected in most every large Veteran's Hospital. As a member of the council of the A.M.A., I served as Chairman of the Sub-committee on Contraception. A heated discussion of the subject had occurred in the House of Delegates. I pointed out to the Committee that it is not a duty of a Medical Society to determine whether contraception is right or wrong. It is the duty of such a society to ascertain the extent of effectiveness and harmlessness of the various methods, so that the A.M.A. may give physicians the correct information on the subject. This stopped all the argument.

Q: There are a number of members of the A.G.A. whom I have not mentioned. I wonder if you had any recollections of Sara Jordan or of Frank Lahey, two Bostonians.

IVY: Both were good friends of mine. Dr. Jordan visited my laboratory in Chicago, also our home. She was greatly respected as a woman, and clinician. She was a good teacher and lecturer at Post-Graduate assemblies. She was friendly and her advise relative to Association affairs was considered to be sound. She was very loyal to the Association and to Gastroenterology.

Dr. Lahey and I must have been together on over 30 post-graduate teaching programs. He was very much interested in my work on the stomach, pancreas, gall bladder and sphincter of Oddi. I would listen to his lectures and he would listen to mine. He was, of course, considered to be one of the outstanding surgeons in his time. And, I heartily agree. He had a reason for everything he did in surgery. This was a great group of men. It was an honor and privilege to know them.

Q: Can you recall any anecdotes about the meetings?

IVY: There are several, but I only recall one at this time. I was involved and it caused everyone to laugh heartily. A paper pertaining to "gastrin" had been presented. A young physician who spoke very well and was very aggressive proceeded to discuss the paper. He stated that "gastrin" must do this, that, and something else. He provoked me to arise and say: "I wonder how the preceding speaker can be so sure what kind of a hormone the intestinal lining should form to stimulate the gastric glands. We are not making hormones. We are not God Almighty. We are not making the body work as we think it should work. We are trying to find out how it works."

No other anecdotes come to mind at present.

THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION:
ITS ROLE IN MEDICINE

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Q: What is your view of the role of the American Gastroenterological Association in Medicine?

IVY: I believe the motive of any medical society should be to promote the discovery and dissemination of knowledge regarding the human body in health and disease for the purpose of providing better medical care. Many physicians quite naturally develop a special interest in one of the functional systems of the body. As a consequence, they organize and establish an institution whereby physicians and medical scientists with a special interest may meet, fraternize and present and publish new knowledge and ideas for mutual educational and scientific ends.

According to my experience, science and its application increases more rapidly because persons develop special interests.

Most all institutions interested in discovery and the dissemination of knowledge begin as a "Club", because of the fewness of the persons with a common object or interest. As a general rule, as the "Club" ages, membership becomes more and more prestigious, and the members become more jealous of their membership. At the same time, the number of physicians and those with the same special interest multiplies. The "Club" then either quits growing or a new institution is established by younger physicians with the special interest to achieve the initial goal adopted by the now "senile club".

The American Gastroenterological Association started as a "Club". Because of the fewness of physicians with a special interest in gastroenterology, it had to start as a "Club". As the number of gastroenterologists increased, it had to give up being a "Club", and had to take on more and more the semblance of a"democratic" institution.

In the American Physiological Society, officers were nominated and elected at the annual business meeting, and every member had the right to give one paper and to introduce another. The minority wanted to move to a nominating committee and to the selection of papers to be presented. Dr. Carlson and I carried on opposition to this change beginning in 1925. Only recently has the number of members increased to the point where a selection of papers is being considered. Nomination of officers are now made by mail, but elections are conducted only at business meetings. For a long time the American Physiological Society was the most "democratic" society to which I had the honor to belong.

I must say that the changes which have occurred in the A.G.A. in recent years have pleased me. If we are going to promote discovery and disseminate knowledge, we must continue in some way to welcome heartily all young physicians who have demonstrated evey in a small way their special interest in gastroenterology. Only a small fraction can make discoveries, but they can attend meetings to be educated and to be inspired to make a worthy contribution to knowledge.

That the recent policy of the Association has been correct is demonstrated by the increase in attendance of the meetings from around 75 to 100 in 1924 to around 3000 in 1969. It is the duty of the members of the Association and its officers to make every physician with a demonstrated special interest in gastroenterology feel that he belongs.

In 1923 or 1924, as I pointed out before, I prepared my paper on the "Phases of Gastric Secretion". My salary did not permit me to go to Atlantic City. Dr. Carlson was going, so he read my paper. I am pleased to observe that the Association is paying the expenses of a few young men or women to present an outstanding contribution.

When I attend the annual meetings, I must say that I have been pleased to see some 30 to 40 former students in attendance. I am sure the same is true of all the older members whose students are carrying on.

Q: Have you seen a change in the balance between the basic and clinical content of the meetings between the 1920's and now? If so, what is responsible for it?

IVY: Yes; there has been a decided change for the better.

Up until about 1940, only about 5% of the papers were contributed by basic science teachers and research fellows. The others were clinical and related to some controversial question of diagnostic or therapeutic value. Several of the clinicians conducted physiological studies. The clinical papers interested me and especially the controversies, which stimulated and inspired me.

I believe the present plan of having at the annual meeting a section on research in basic science, and a section heavily weighted with clinical subjects, is excellent.

Q: How would you evaluate the role of the A.G.A. in shaping gastroenterology as a medical specialty today?

IVY: I believe the A.G.A. has contributed to the development of its specialty as much as any other specialty. This, of course, speaks well for the teachers of the present generation of gastroenterologists. The development of a gastroenterological subspecialty in the American Board of Internal Medicine gave the gastroenterologists of one and two generations ago a decided boost.

The appearance of large hospital clinics, like those in Germany, France and Britain, in the U.S.A., provided the first boost to gastroenterology. Most all large hospital clinics had a section on gastrointestinal disease. This was the result of the actions of such men as Spallanzani, Bernard, Heidenhain, Pavlov, Ewald, Hurst, Beaumont, Cannon and Carlson.

Q: Could I ask you about the rule of the A.G.A. in research? Do you think the A.G.A. itself has played a role in the increase in research in gastroenterology?

IVY: The Association encourages research by having a meeting or an open forum, by having a journal of its own, and by providing a source of ample funds, such as the National Institutes of Health Service. The research is done by the individual.

Q: Yes, that is a well made point.

IVY: The A.G.A. has provided a forum, and it has been a good one. From 1920 to 1955 there was a feeling that it was too difficult to get on the program. The plan of today should have been established in 1935.

When I was President in 1940-41, the Association did not have a journal of its own. It had been too cautious and was afraid it would loose money, and could not obtain enough papers for publication and could not obtain enough subscribers. I wrote some 60 persons to ascertain if they would send me a paper for the first or second volume, and if they would subscribe. Then, with library subscriptions and the membership of the G.I. Section of the A.M.A., I knew we could obtain enough papers and subscribers. It was evident that the Association could have a flourishing and profitable Journal because the disease of every physiological system manifests symptoms referable to the Alimentary Tract. Furthermore, I had been a member and Chairman of the Board of Publication Trustees of the American Physiological

Society for several years, and I knew that a journal would break even with 1000 subscribers, and if the journal would accept ethical advertising, they would make enough money to finance a Fellow in Gastroenterology in a medical school. This latter desire had been discussed since 1925 at business meetings. Williams and Wilkins felt as I did and finally gave the Association a contract, so that it would pay all losses for the first 5 years, divide profits with the Association annually and if, at the end of 5 years, the Association should wish to buy the journal, the company would sell it to the Association for the profits it had paid the Association. This made the journal, "Gastroenterology", an assured success.

In the Fall of 1942 at night at the Naval Medical Research Institute, Bethesda, Maryland, where I was the Scientific Director, I put together all of volume I.

The Association now provided a forum and a journal. Funds for research had to be obtained. A private benefactor had been looked and hoped for in vain. The Government had the funds and the Public Health Service had already established Institutes for Cancer, Infectious Diseases and Nutrition. Congress was becoming interested in medical research.

In 1944, when I became a member and later Executive Director of the National Advisary Cancer Council, I learned that the U.S.P.H. was considering the advisability of setting-up an Institute for other important diseases following the pattern of the Cancer Institute.

At that time I tried to set-up an effective liason between the U.S.P.H.S. and the Governing Board of the A.G.A. to explore the idea of an Institute of Gastroenterology. At that time the idea was strategically immature. The same was true when I tried in 1950. Finally, an Institute on Metabolic Diseases, including gastroenterology, was established.

Then "plenty" of money, some say too much, was made available. With "plenty" of money available, there was suddenly a surge-like increase in gastrointestinal research. It should be added that about 1935 the Association undertook a survey of methods for the measure of enzyme activity. This is the type of team work which the Association should foster. The survey was greatly handicapped by lack of funds.

With this historical review, it is evident that the Association is now attending to what I consider to be its major functions.

Q: Would you comment on the current status of education in gastroenterology today?

IVY: The physiology of the alimentary tract is not well taught in most of our medical schools today. This reminds me of the experience of Dr. Leon Goldman, who was Professor of Surgery and later Dean of the Medical School, of the University of California. When he was an Associate Professor of Surgery in charge of the teaching courses in surgery, he took a year's leave and attended my courses in physiology and the anatomy and physiology of the signs and symptoms of disease. He also conducted research with me. He had published several clinical research papers. He did this because he had found that the students came to surgery poorly prepared in the physiology of the alimentary tract; yet, more than one-half of the patients with disease and who were later operated had disease in their alimentary tract and its adenexa. He then visited the Head of the Department of Physiology and inquired: "Do you know that the students from your department come to us in the Department of Surgery unprepared in the physiology of the alimentary tract?" The Professor of Physiology said, "Yes, I am not surprised, because in our course in medical physiology we do not devote any time to the alimentary tract." The surgeon asked, "Why"? The physiologist replied, "No one on our staff knows anything about the alimentary tract".

At the 50th anniversary of the American Physiological Society, as Past-President, I made a speech on the subject of your question. I said in effect that in view of all the money available for research, research can be, and in some cases is detrimental to one's teaching duties as a staff member of a medical school. <u>I stated that when one holds a teaching position their first duty is to teach, their second duty being to try to advance knowledge</u>. It should not be forgotten that students in a medical school will take care of sick people, and that the only basic information on which they will build their career is that which they secure in their courses in physiology and biochemistry. They have the remainder of their lives to enhance their knowledge and skill of the practice of medicine and surgery.

Because so many teachers of physiology have devoted undue time and interest to research, the teaching of the physiology of one or more functional systems has been neglected, and more and more physiology has had to be taught by clinicians. As a result the hours of teaching of one or more of the basic sciences have been reduced and added to the clinical departments. I indicated that between the years 1935 to 1960, more than half of the physiology of the alimentary was taught by surgeons and internists. That was true for about 75% of the medical schools. I can not state what has been the case since

1960, because I have not been in touch with medical education. I have noted, however, that in a few medical schools it has been proposed that elementary basic physiology be pushed back into college and only applied physiology be taught in medical schools by clinicians.

There was a time when teachers of physiology offered a balanced course and were able to keep up-to-date with the advances in physiology of the blood, circulation, respiration, digestion, metabolism, endocrinology and nervous system. I covered all of these symptoms for from 1917 to 1953. Numerous other physiologists kept themselves prepared to teach all these subjects. However, it is much more difficult to keep up-to-date with all these subjects than formerly, and the expense prevents most medical schools from employing a specialist to teach each system. <u>So, the best plan would be for the clinical specialist to ascertain what is actually being taught in physiology and biochemistry about his subject and then to supplement any obvious deficiencies</u>.

There is an outstanding defect in the teaching of many of the basic science teachers, when they give a course in physiology to medical students. This defect is to emphasize unduly the subject of their current research interest. In biochemistry, for example, they try to make carbohydrate or protein, or enzyme, or nutrition chemists out of their students. As a result, many medical students do not know the physiology and biochemistry they should know.

Q: Has the current increase in research effected teaching in gastroenterology?

IVY: I believe it has improved the clinical teaching and practice of gastroenterology. From what I have learned by talking to others and attending discussions on teaching, it is very doubtful whether the teaching of the basic physiology of the alimentary tract has been improved.

The greatest and most important task of a teacher in medical school is to select the subject matter to present, to emphasize, and to render lucid. Since the student is with the teacher for such a short period of time, the teacher should not waste any of his time.

Most text books are semi-reference books. From these books, the teacher should select, emphasize and clarify the important essentials. This is what all the good teachers whom I have had, did. At the start of the course, I have given my students a list of some 200 to 250 questions to be answered in the course and which they must be able to answer at the end of the course and in the practice of medicine.

Q: Do you think that there has been any change in the prestige of the teacher in the past generation?

IVY: No, Sir! Good teachers are born and self-made. Percentage wise there are as many good teachers today as in the past. Unfortunately, some of them do not want to teach. I have found that good teachers with a few exceptions are respected by the majority of students; but, not necessarily by their fellow teachers.

The requirements of a good teacher are three in number:

(1) To keep school, that is, to require punctual attendance, to make assignments, to give a weekly short written examination, grade and return the paper, and tell the students that the results will make-up one-third of their final grade; otherwise there is no need for a school.

(2) To make students work and like it; or to inspire. This is an extra-dividend, because many teachers can not do this.

(3) To cultivate insight or the ability to see the relation between things, or to think logically and analytically. This also is an extra-dividend. Only about 20% of medical students can do this.

I will illustrate by a situation in which Dr. Carlson was involved. He had complained about the inferior quality of students who had been selected to study medicine at the University of Chicago. So, the Admissions Committee gave Dr. Carlson the job of selecting the next first year class. His class did well in anatomy, where memory primarily makes a good student, because there are few open questions and the information is well organized. Then they came to physiology, and Dr. Carlson gave this class the first course in physiology on the blood, circulation and respiration. Someone else taught the laboratory work. Dr. Carlson met the class three times a week and gave an interesting talk on some subject. He did not take the roll; he did not present organized information; he expected them to read a textbook on the blood, circulation and respiration; he did not give examinations weekly or bi-weekly. He then gave them a final examination. He failed 60% of the students, most of whom depended on a passing grade to receive the B.S. in Medicine degree. There was a great flury at the University. Parents were there to see their sons graduate. The incident received coverage in the University newspaper and Chicago newspapers. The students and parents asked him to meet with them. They wanted Dr. Carlson to change his grades.

Dr. Carlson said: "It is all my fault. I thought the student's I selected would learn without being goaded and spoonfed." I cannot raise the grades; it would be dishonest. They must know the subject matter of the course to make good physicians. To raise the grades would not give them the knowledge they should have. So, they must take the course again."

Dr. Carlson had great prestige as a faculty member, as a teacher of graduate students and of freshman college students. However, medical students are given so much reading material that they would have to read night and day to cover even one-half of it. So, the important subjects have to be selected and organized, explained, and made reasonable, lucid and coherent. To prevent cramming, a weekly examination is required.

We must recall that sleep is the most normal physiological condition. To keep people alert and working consistently in most all cases, they must be given definite goals and goaded frequently. Everybody is lazy; some more than others.

Most students have a high and lasting regard for teachers who show interest in stimulating them to learn and to like the subject matter to be learned. I have observed that the great majority of medical students like to learn and understand any information which may help or enlighten them in caring for the sick.

To gain prestige and to receive a better salary in the University it is first necessary to perform attractive research. Being a good teacher helps. I know that the purchasing power of the wage of a young teacher in a medical school today will buy much more than in 1917 to 1925. The Ph.D., M.D. graduate from 1918 to 1936 would be offered only $2,000 to $3,000 for teaching for 9 months. As an assistant to a physician or as a member of a clinic, the offer was from $10,000 to $25,000. (In 1930 I was offered $40,000 a year by a hospital clinic.) I advised my Ph.D. graduate students to obtain the M.D. degree. I seriously told them they would do better if they had a "union card" and the clinical knowledge would make them a better teacher for medical students.

I feel sure that the prestige of the full time clinical teachers of medicine and surgery and gastroenterology in medical schools has increased.

I believe a specialist should keep up with the progress in the basic science of his field in so far as is possible. This is much more true of gastroenterology than it was even in 1940. Prior to 1940, the specialists who were interested in basic science were the neurologists, surgeons, cardiologists and gastroenterologists. I am pleased to see so many young men who have made contributions to basic science attend the meetings of the Association. This undoubtedly adds to the prestige of the Association. At the Philadelphia meeting in 1968, I was asked if I thought there was over-emphasis on academic or basic science in the program. But as I have said before, the clinical program must not be neglected. It can be enlarged perhaps.

Q: Another role that the A.G.A. has occasionally taken is attempting to perform research itself or organizing cooperative ventures, such as the "Study of Peptic Ulcer". Do you feel that that is something which a specialty organization can do effectively, or do you feel that it is difficult to do?

IVY: The answer of that question should not be generalized. I know because I served on 5 granting committees in Washington, during the war, and have served on several State agencies and private foundations interested in medical research.

Each proposal for cooperative research has to be considered on the basis of its scientific and educational merits; and its expense in time and money.

I include symposia under your question because symposia constitute "cooperative library research" for the purpose of summarizing the current status of a subject of general interest. This is a duty of any Association of scientists and medical practitioners. I believe it is legitimate to expect the membership to subsidize the expenses, provided other sources can not be found.

Most research published today has had 2 or more persons as authors, which indicates that the research was cooperative. <u>In this connection it must be recalled that new ideas or discoveries come from the mind of individuals</u>. Of course, the work of many individuals forms the background of most new or even serendipitous discoveries. In fact, most research conducted today in universities, industrial laboratories and governmental institutions is cooperative in nature. This is because of the prime motive of cooperative research.

The <u>prime motive of cooperative research</u> is to expedite the securing of an answer to an important problem of practical interest or of potential practical interest. There is no other reason to be in a hurry, and to obtain the collective thinking and assistance of persons of experience. However, while a large and expensive project is in progress some little known young person outside the cooperative project may discover the answer or an important clue to the answer. This indicates that grants-in-aid for one man research should not be neglected by spending all the money available for cooperative research.

This recalls an incident which occurred at the Naval Medical Research Institute during World War II, where I was the Research Director. I asked Lieutant McLimans, a young man who had been working on influenzal virus, to ascertain if the drying of blood plasma would destroy the influenzal virus. He proved that it did. "Scrub Typhus" appeared in the Marine Corps in Burma. There was no treatment other than supportive. I suggested that he try methylene blue because I thought it might be toxic for the virus. We formulated a proposal and sent it to the appropriate committee in the Navy for approval. The committee rejected it. I called the Admiral and asked "Why"? The Admiral said: "The Committee of Scientists (scientists, mind you) had said the search for the treatment was a job for experts". I said: "Admiral, will you please ask the Committee how the experts got that way". The project was approved. This treatment worked to some extent in mice, and was the first to be tried for effectiveness in the field by a cooperative research team.

I have previously referred to the first cooperative project approved by the A.G.A., namely, to review enzyme methods and select the best methods to recommend to the Association. I was the Chairman of the Committee, without any money to defray expenses. All Committee members were interested, but their chemists were too busy to try the tests sent to them. There was no traveling expense money to render it possible to visit my laboratory, where the work was going on, and I had to depend on a chemist who volunterred to work in his spare time without pay. We made a good start, but we could have done much better if we had had some expense money. This, and other incidents I could cite, show that if a question is important enough to be expedited, then adequate funds should be supplied.

This means that if the Association believes there is a problem sufficiently important to be expedited, then a cooperative research project should be designed, provided the Association can secure adequate funds. Adequate funds could hardly be expected to come from the members of the Association.

The funds for large cooperative research funds now come from government and private sources. Money from private sources, according to current practice, comes from wealthy foundations, such as the Ford, the Rockefellar, and others, or from Medical societies or foundations set up to do cooperative research on a single disease, such as the American Cancer Society, the March of Dimes Foundation, the Arthritis Foundation, etc.

Most of the research being done by the A.G.A. members is now subsidized by Governmental Agencies. However, there are foundations for specific diseases of the alimentary tract, such as the Fibrocystic Foundation, the Ulcerative Colitis Foundation, etc. I do not know of a foundation for peptic ulcer.

It is generally easier to raise money from the public for the prevention and/or cure of a disease. In the case of peptic ulcer, the name would be: "The Peptic Ulcer Prevention Foundation". This could be a foundation of the A.G.A. The foundation could be set-up for collecting money like the March of Dimes. There are at least 10,000,000 adults to be solicited as contributing members of the Foundation. This can be made a success with the right kind of promotion. The only other alternative is to remain as we are. Of course, the "Foundation for the Prevention of Peptic Ulcer" should not be permitted to interfere with the present program of the Association. The foundation would report and be responsible to the Association.

As I have stated frequently, the most practical way to prevent peptic ulcer would be to discover some non-noxious substance to take in the form of a pill before and between meals to suppress decidedly the formation of acid by the stomach. Here is a specific goal to which most ulcer victims would gladly contribute.

Funds for research by individuals must be kept available. It has been said that most of our new discoveries having been the result of the adventure or exploratory research of individuals. When I was Director of the Naval Research Institute, I told the scientists that our <u>chief duty</u> was to answer questions from the field which would save or prolong the life of the men in our fighting forces. However, if any one developed a new idea which he was interested in exploring, he could do so on his own time. If someone had a new idea which needed testing or exploration and which would not be approved if submitted to the approving committee, then the exploratory research was done under my approval. When enough research had been done to know the probable end result, it was submitted for approval to the approving committee. So we had two catagories of research projects, one "exploratory projects", and the other "approved projects", or "fashionable projects". In my own laboratory each graduate student had a "bread and butter project", and a "your own project". It is very important to keep funds available for exploratory research.

Committees for approving and disapproving projects and for evaluating the value of a new discovery are sometimes necessary evils. The history of science shows that the proposal of every new idea, especially in medical science, generated a controversy, especially if it involved the treatment of disease. Committee opinions on the promise of a new discovery or idea have been notoriously wrong. This statement should be printed on a centerpiece for placement at the center of the table around which a committee sits.

Q: You spoke of exploratory research and of controversy. What role does controversy play in the advancement of medical knowledge?

IVY: If you read our book on "Peptic Ulcer", you will find much controversy and controversial literature. In the book we tried to organize this literature to make it constructive. Sometimes the controversy was constructive, and it had to happen, because of the nature of the subject and the ignorance surrounding the defensive attitude of authorities and hierarchies, religious, professional and "scientific", when such were involved. A hierarchy cannot afford to be shown to be wrong or to lose face, and saving face becomes the prime motive, when to ascertain the truth should be the prime motive. In this instance destructive criticism reigns supreme and submerges any constructive criticism. Destructive criticism rarely assists in the search for truth. When this condition exists, time is the only successful therapist.

Q: That is an interesting way of putting it.

IVY: Controversy is a two-edged sword. It has value in that it causes further research, unless further research is suppressed by an authority or a hierarchy which fears the truth. The disadvantage is that controversy frequently and unnecessarily delays the establishment of the truth, especially when an important truth may be at stake.

For example, Von Mering and Minkowski in 1889 discovered extirpation diabetes. In 1903, Minkowski reported to a medical meeting that he had prepared an extract of the pancreas which would decrease the blood sugar level. He was critized severely and became discouraged. Thus, in 1912, E. L. Scott confirmed Minkowski and criticism discouraged him. Then, Banting, Best and Collip in 1922 established the fact, first reported 20 years earlier. Looking back it seems surprising that a cooperative effort was not made in 1903, to establish without delay the truth or falsity of Minkowski's claims. In the case of penicillin, Fleming's discovery stood on the shelf for 12 years, while he was called a "quack". The work which Howard Florey, who was a student of mine, did to establish its clinical use would not satisfy today the Food and Drug Administration requirements. Again looking back, it is surprising that Fleming's very important claims were not immediately researched by others to ascertain their truth.

Q: Dr. Ivy, what do you believe to be the best thing a College, University or Medical School can do for a student?

IVY: Several years ago the University of Chicago sent a questionnaire to all Alumni who had received an Alumni Distinguished Service Award. The question you have asked was in the list of questions. My answer was: "The best thing the University of Chicago did for me was to give me a place to work in an inspiring environment".