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# The Physiologist

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Orr E. Reynolds, Editor

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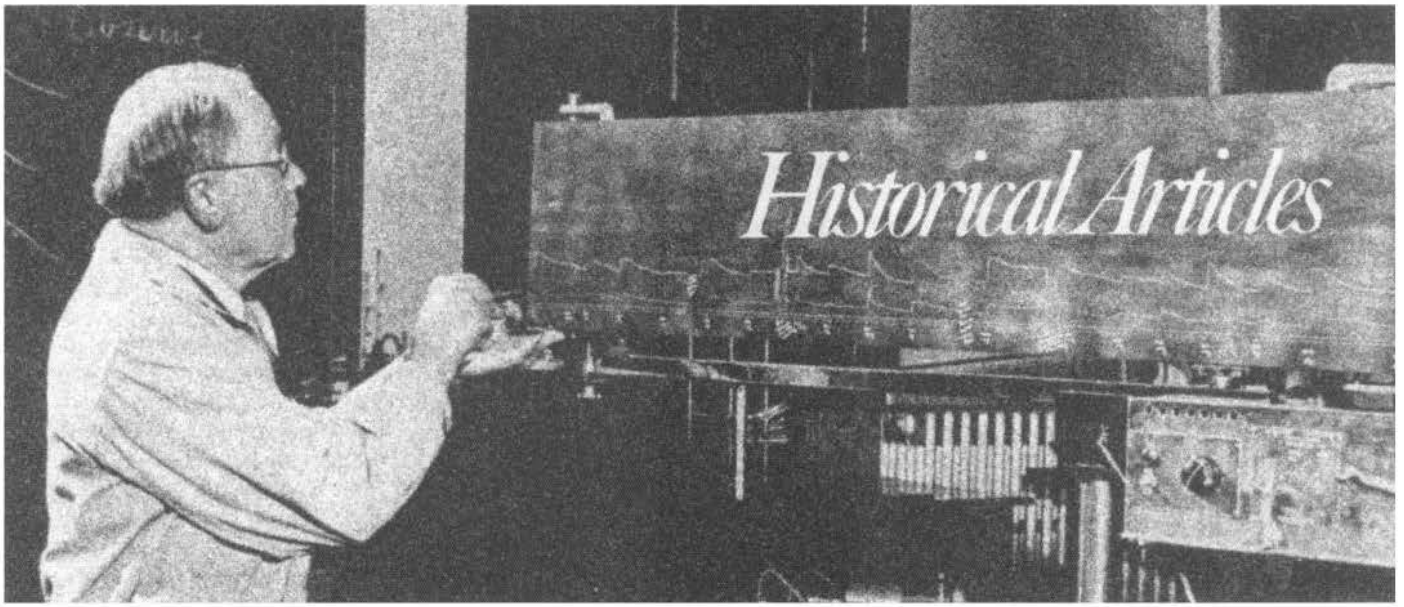


# GEORGE H. WHIPPLE
# or
# HOW TO BE A GREAT MAN WITHOUT KNOWING DIFFERENTIAL EQUATIONS*

**HORACE W. DAVENPORT**
William Beaumont Professor of Physiology
The University of Michigan

The subtitle of my talk tonight is "How To Be a Great Man Without Knowing Differential Equations." Every year I struggle hard to find a topic for my next talk, and I am already thinking about next year, assuming there will be a next year. I was describing these seminars in Göteborg last spring, and the topic for tonight suddenly occurred to me then. So you see I have been planning it for a long time, and any deficiencies are not for lack of planning.

I am going to tell you about the first American to get the Nobel Prize in Physiology and who got it for work published in the *American Journal of Physiology*.

Who was Whipple? Does anyone know? I could show you some pictures of him in a book by George W. Corner (1), of whom I will speak later. One picture shows him receiving the Prize in company with two other Americans, George Minot and a man named Murphy. The picture also shows another recipient, Luigi Pirandello. Do you know who he was? Playwright; the nature of reality. I mention him, because I managed to get him into the fourth edition of my *Physiology of the Digestive Tract* (2), along with T.S. Eliot. That took some doing.

The work for which Whipple got the Prize is *Blood regeneration in severe anemia. II. Favorable influence of liver, heart and skeletal muscle in the diet.*, by F.S. Robscheit-Robbins and G.H. Whipple, *American Journal of Physiology* 72:408-418, 1925. A question is: Who was F.S. Robscheit-Robbins? I'll talk about that later.

If you studied medicine, you know there is a Whipple's Disease. Whipple was a pathologist by trade, and every pathologist has to have a disease named after him. It is an extremely rare form of malabsorption which gastroenterologists know about but which is of very little importance. If you're a surgeon like my postdoctoral fellow, Gordon Kauffman, you will know there is a Whipple's Procedure, but that is another Whipple altogether. What Whipple showed is in the summary of the paper: feeding beef liver in severe anemia is associated with maximal regeneration of hemoglobin and red blood cells. So, what Whipple showed is that liver is good for blood. I will return to that, but first I want to talk about my connection with Whipple.

There are two connections. The first was in 1939 when I got my Ph.D. in biochemistry at Caltech. The ambience of that will show you why I talk about differential equations. One was supposed to know them and to know thermodynamics. I got my first postdoctoral job in Whipple's Department of Pathology; how and why will be explained later. In my curriculum vitae you will see that I was a Fellow in Pathology. I have actually done an autopsy. I once stated that in the presence of our Professor of Pathology, and he said that is more than some pathologists have done. I won't tell you how I came to make "the usual Y-shaped incision."

I had very little to do with Whipple when I was in Pathology at Rochester. The reason was that I was a very junior person in a very distinguished department, and Whipple wasn't around very much. When he was around he left at noon. Whipple was then very senior, and he was involved in many other things such as salmon fishing. He had a river in Nova Scotia, and he had a farm in South Carolina. He had a lot of other avocations, so that he really wasn't present in the Medical School very much although he was a professor and director of the Department of Pathology.

*Derived from a Seminar on the History of Physiology given for graduate students in the Department of Physiology, The University of Michigan, September 24, 1976.

He was also Dean. He ran that very large and important school in an afternoon a week with the help of a secretary. You can contrast that with the way medical schools are run now, with a large number of office boys, all with the title of Associate Dean.

Another evidence that I had very little to do with Whipple is that he thought my name was Davidson, and I have gone down in the history of Rochester as Dr. Davidson.

I was rather contemptuous of Whipple. I didn't know, and I didn't appreciate, his good qualities. I was young; I had just come from Caltech; but I was really quite ignorant. This a characteristic of youth. I will point this moral here, because you are all quite young, too, and you may be contemptuous of persons who deserve a little better consideration from you.

I did some good work at Rochester, and I published four papers from there. Two were purely descriptive. Two were theoretical, and both theoretical papers turned out to be absolutely and totally and completely wrong. That didn't stop them from being reasonably good papers. I won't talk about that, for it is another subject altogether. I gave a seminar about my work. It contained some equations, not differential equations, but simple algebraic equations. Whipple was present, and Whipple demonstrated that he didn't understand what I was talking about.

In general, there are two kinds of scientists. One kind is highly abstract and theoretical. These are extraordinarily important for science, as I need not point out. The others are very practical, the plumbers, the ones who work with their hands. They, too, can make important contributions, and one of the speeches I make is how one can do absolutely classical work without having any ideas at all. This is frequently done, and Whipple did it sometimes. I'm not saying that he didn't have ideas; he did have them, but they were not abstract. His kind of person, the kind who doesn't know differential equations, can be remarkable contributors to society, and they are the ones who tend to be academic statesmen. Whipple was very definitely an academic statesman, but you young persons don't realize how important academic statemanship really is. Its success or failure makes your environment what it is.

The other connection is through Corner's biography of Whipple. I bought a copy when it was published, and I have pasted into my copy a letter from Whipple to me as well as one from Corner. When our boy Andy was admitted to the University of Rochester Medical School I sought a copy of the book for him, but I found it was out of print. Half expecting what would happen, I wrote to Corner asking if he knew where I could get a copy. He wrote back: "I just happen to have a copy which your boy can have," and he signed it for Andy. Andy read it, so he knew about Rochester before he got there. Andy was working at the Rockefeller then (and it's great to be able to say all the rest of your life: "When I was at the Rockefeller..."), and he read all of Whipple's papers. When he got to Rochester, Whipple was still in reasonably good shape, and he too signed the book for Andy. Whipple was, of course, very old, and he underwent the inevitable decay. He died at 97, and as he died, Andy was listening to his heart. So there is the second connection.

Whipple was a Vermont Yankee with all that that means. He was a practical man, as I have already said, and like a Vermont Yankee, he was frugal. This shows at Rochester. Those of you who have visited the place know what the older parts look like, and that shows Whipple's frugality.

Whipple went to Yale, and at Yale he was an athlete. There was a story floating around Rochester to the effect that when Whipple was at Yale he played semi-pro baseball in the summer under an assumed name, was caught and was thrown off the Yale team. I doubt that was true, but Whipple certainly liked athletics. When he built the Medical School at Rochester, he built a gymnasium for staff and students. One looks around other medical schools and has a hard time finding a gymnasium. Among his other ideas, Whipple thought medical students ought to have vacations, and they do at Rochester. Again, one looks at other schools and finds that is not the case.

Whipple went to Hopkins, and he graduated in the class of 1905, the last year that Osler taught there. He became a pathologist, as I have said, and this means that he was a student of William Henry Welch (3). I am not going to talk about Welch, except to say that he was the great man of American Medicine. He was a statesman of enormous importance. As Dean and Professor of Pathology he conducted a stable of future deans and pathologists. When some school needed a dean or a pathologist, the next man on Welch's list got the job. This was common phenomenon. At Harvard, for 30 years, the next man on Cannon's list got the job in physiology. At Yale, the next man got the job in biochemistry.

At Hopkins Whipple found his disease doing an autopsy. He also spent some time in the Canal Zone as a pathologist, but this is of not much importance. Then he went to California. At that time the only medical school of the University of California had its clinical years in San Francisco. There was a foundation, the Hooper Foundation, which provided a research job for a scientist. Whipple took the job as Director of the Hooper Foundation, and there began his work. To help him, he had a technician, a German woman named Frieda Robscheit. She is the F.S. Robscheit-Robbins who appears on the paper that was the genesis of a Nobel Prize.

Whipple became dean of the medical school in San Francisco. The school had its problems, one of which was the separation from the preclinical departments in Berkeley. By that time (1910-1920) the University of California had become one of the really great universities in almost any subject you want to mention: chemistry, physics, psychology, and the rest. Among the great departments were one or two preclinical ones. The department of Anatomy was dominated by a man named Herbert Evans (4). Herbert Evans was a great endocrinologist, and he was also a very peculiar man indeed. That is another story. In his department was a very junior endocrinologist named George Washington Corner, the first primate endocrinologist in the United States. Ovulation in monkeys was his subject then.

Early in the 1920's Whipple was invited to go to Rochester, New York, to found a medical school attached to the University or Rochester. I speak here about medical education in the '20's in this country. We deplore the '20's as the age of frivolity, of F. Scott Fitzgerald, but we forget that among the many accomplishments of the jazz age was the foundation of modern medical education. Contrast that age with the present we are so proud of, an age of the degration of medical education marked by the deliberate proliferation of inferior schools. In the '20's the opposite process was going on, largely under the influence of Abraham Flexner and backed by Rockefeller money. New schools were founded; Duke was one, and Rochester was another, very good schools indeed. Some of the old ones were enormously improved, Iowa, Minnesota and so on. One object was geographical distribution. Rockefeller money, namely Flexner, thought there should be a good school in upstate New York. Syracuse was inspected and found wanting. Flexner decided instead to try to found a school in Rochester. Now, upstate New York, as some of you know, is a peculiar place in many ways. Parts of it are very beautiful. The city of Rochester is a remarkable

city, first, for Eastman Kodak Company. Eastman had a vast amount of money, and he had already displayed a philanthropic bent by endowing the Eastman School of Music and the Dental Infirmary. He was ripe for being touched for a medical school. But there were many other high-quality industries in Rochester: Bond Clothes, Bausch and Lomb, Taylor Instruments, the manufacturer of ball bearings. It is a high-class industrial city with skilled and intelligent workmen. Flexner had a foundation on which to work, a reasonably good, small private university, the University of Rochester, with a good president. He was Rush Rhees. When you fly into the Rochester airport from the northeast you will just miss the stone wedding cake on the top of the Rush Rhees Library which commemorates him.

This is another story I won't talk about: how good places get going, the necessary combination of outside talent and money with inside talent and money. This is a subject you aren't interested in at present, but if you do go into academic administration you will become interested in why some places are good and some are not.

Whipple began in the early 1920's to build a medical school in Rochester with local money and with Rockefeller money. He bought a farm way out in the country, the Crittenden farm which is why the school is on Crittenden Boulevard. The first thing he built was an animal house. This is very important for two reasons. One is that he needed it for his research, which I will get to. The other is that in the early 1920's animal quarters were sinkholes of creation. You have no idea what animal quarters were like before Ben Cohen and those like him took over. When I was at Penn I couldn't go in to the animal quarters, because I would vomit. They were frightful, and that was a general characteristic of animal quarters. You pay for Ben Cohen's help, but it is worth what you pay. Whipple built what was then a high-quality animal quarters. He moved his faculty into it and then built the school. It was the original building from which the rest grew.

If you have seen Rochester you know that the medical school and the original hospital are one building made up of repeating units. Repeating units meant that forms could be moved from one unit to the next to save money on lumber. There were no traps on the sinks. Whipple managed to get the building code changed (he was skillful at things like that) so that he could save money. When I was at Rochester, the way to kill the man in the lab below was to pour ether down the sink, turn on the hot water and then throw a match down the sink. This was guaranteed to be effective, but I never tried it. Another piece of frugality was that there were no locks on the laboratory doors. Those of you who know my attitude toward locks know how much I appreciated that. If one trusts a person enough to have him work for you, he shouldn't be barred by a lock, and I deprecate the current atmosphere which makes it necessary to lock doors. There were other pieces of frugality such as no paint on the walls of the preclinical parts of the building, but I won't enumerate them all.

Whipple assembled a very good small faculty. All the persons he got turned out to have very distinguished careers. The man who ran the hospital was Nathaniel Faxon. That doesn't mean anything to you, but I knew him in his old age. He lived in West Falmouth on Cape Cod, but before that he ran the Massachusetts General Hospital. The bacteriologist was Stanhope Bayne-Jones. Corner was his professor of anatomy. You wouldn't recognize the surgeons and internists. He had, I believe, only eight departments, in contrast to the 57 or whatever it is that Michigan has. There are advantages in having a small number of departments.

Whipple's professor of physiology was Wallace Fenn who was 31 when he was hired. I think you know that when he died he was definitely the premier American physiologist. The last time I saw Fenn we had dinner together at the Michigan League. He said: "We had nothing else to do but research." This was the days before grants, and Fenn did really distinguished research without Federal grants.

Whipple had many progressive ideas. I've already mentioned the gymnasium and vacations. Another was to provide fellowships for medical students who wanted to drop out for a year to work in one or another department. Most of you are too young to remember that this was a great new idea of the N.I.H. back in the '50's some 30 years after Whipple had it. There were two students in Pathology; the reason was that a man who was Whipple's boy was made. Quite properly. This is one of the reasons that, over the years, Rochester has had such an impact upon American academic medicine.

One of the men who had students working with him was Corner. I knew Corner very slightly, chiefly by having lunch with him in the faculty cafeteria. I have the distinction of having broken his quartz transilluminator. This was the days before the plastic ones. I was trying to see whether the oxyntic cells of a rat's gastric mucosa accumulated a dye. I broke the rod, but he didn't seem to mind. He had a medical student working with him between the freshman and sophomore years, a boy named Willard Allen. At that time it was known that estrogens had something to do with the development of endometrium, but it was obvious there was something else. That something else was progesterone, and it was got out by a student who had stopped to work with Corner. He could do that because Whipple provided the opportunity. Allen became the gynecologist at Washington in St. Louis. He had a very distinguished department. I point out here that you endocrinologists must know the difference between Edgar Allen and Willard Allen. If you don't you have no business being here. (Who was Edgar Allen? He, too, had a connection with St. Louis, but St. Louis University, not Washington in St. Louis. He was professor of anatomy there. Because Papanicolaou had shown that you could tell the stage of the estrous cycle of a rat by vaginal smears, Edgar Allen and the professor of biochemistry, a man named Doisy, went down to the slaughter house to get a bucketfull of pigs' ovaries. What did they get out? It was theelin, wasn't it?)

Let's get on with Whipple's research. Much of it was ephemeral, as, indeed, most research is ephemeral. Most research has absolutely no consequence except being published and then forgotten. The question he asked at the Hooper Foundation was: "What supports the formation of hemoglobin?" The method he used was a very simple one. First, he got chronic dogs. Again, you don't realize how important it is to have chronic animals, because you always have them. In the old days, you didn't They would all die of some disease before you were finished with them. You only used acute dogs which you could kill the day after you received them. They would smell frightfully, for they hadn't been bathed and perfumed, and they hadn't been immunized. But Whipple did use chronic dogs. He had a kind of hunting dog, and he produced anemia by the simple process of bleeding them twice a week. He would get their hematocrit to some standard level, somewhere near 30% (a dog's hematocrit is normally 50%), and the dog would be anemic. He kept on bleeding the dog to keep the hematocrit at 30%. It's obvious that the law of the conservation of matter applies here: the amount of hemoglobin you take out in a week to keep the hematocrit at 30% is the amount of hemoglobin the dog made the week before. It's a very simple idea, indeed.

Whipple had a kennel of "standarized biological machines." There are stories about these dogs. There was a lot of huntin', shootin', and fishin' around Rochester, and these dogs were

hunting dogs. Someone took one out hunting, a dog with a low hematocrit. He got 5 miles out in the woods, and the dog collapsed and had to be carried all the way back to Rochester.

This very simple method established the requirements for the formation of hemoglobin. You feed the dog something and see how much hemoglobin it makes. You feed it liver . You feed it brain. You feed it skeletal muscle or whatever you want. But first you have to feed it a minimal diet. Whipple worked out what was called a salmon loaf. I'm not sure why it worked, for salmon contains a lot of high-quality protein. He found, for example, that if you mixed the salmon loaf by machine, it was better for hemoglobin than if you mixed it by hand. I think the reason was that the machine was rusty and supplied the dogs a little more iron. I don't think Whipple really ever sorted out all the requirements.

Later, at the time I was in Rochester, the fundamental, pioneer work on radioactive iron was being done in Whipple's department by a man named Paul Hahn, and I recommend that classical work to you (5). It is, by the way, one of the reasons I never put my name on papers of my students or collaborators unless I have done a substantial amount of the work myself. When the papers were written by Paul Hahn, he practically had to hog-tie the old man to read the MS. The authors are Hahn, Ross (a Fellow who was my friend), Bale (who built the counters) and Whipple, but they were cited as "Whipple has shown that ..."

Whipple fed liver to his dogs, and he found liver was best. The dogs made more blood. Now, here is a good question for a preliminary examination: *Why* is liver good for blood? You can tick off the answers yourself, but it took a long time to work them out.

Let me stop a this point to pay a tribute to Frieda Robscheit-Robbins. She was the woman who saw that Whipple's research on blood regeneration was done and done right. She had little formal training; she started out as a technician who knew what she was doing. The University of Rochester gave her a Ph.D., so she was Dr. Robscheit-Robbins. When I was at Rochester I had very little to do with her, for I was very junior and she was very senior indeed. But I did have something to do with her when I was President of the American Physiological Society and she was President of the Society for Experimental Pathology, which is pretty good for a technician without much formal training. The older persons who attended Federation meetings in those days will remember her. She was always beautifully dressed, and her hair was elegantly coiffeured. She wore striking hats and real diamonds. She was a lady of considerable presence.

Whipple's demonstration that liver is good for blood was picked up by George Minot. It is perfectly obvious he was a Bostonian, for Minot is one of those names like Cabot (6). Minot was a Harvard hematologist. He was also a very fragile diabetic, and he just made it to 1923. You don't realize that the diagnosis of diabetes was a death sentence before 1923. He was interested in pernicious anemia. Pernicious anemia is called pernicious anemia because you die of it. Your hematocrit keeps going down until you fall over dead.

I did have some relations with Minot as I will show you later. Here is something from him I am saving for my children. I sent him some reprints of my papers, and I got this note from "Dr. George R. Minot, 71 Sears Road, Brookline, Massachusetts. Dear Dr. Davenport, I received at the Thorndike today the copies of your recent papers. I have just read them this evening. They are first rate. Thank you very much for sending them to me. Sincerely yours, George R. Minot. July 1, 1940." I show you this not to point out that my papers were first rate. As a matter of fact, they turned out to be preposterously wrong. But I point out that a man who was a Harvard professor, a very distinguished hematologist, a man with a Nobel Prize, could take the trouble one evening to go to his desk, pull out a piece of paper and write to a very junior person a note of thanks and appreciation. That's something to remember, that it never does any harm to tell a person what you think, especially if it is something good, as he did here.

Minot, as I have said, was interested in pernicious anemia, an incurable disease. He read Whipple's paper in the *American Journal of Physiology,* and he said: "Aha; if liver is good for dogs, maybe it's good for men. Let's try it on patients with pernicious anemia." He fed them raw liver, at one-half pound a day. I am told that some of the patients, after a while, would rather be dead than eat a half pound of raw liver a day. The end result was this paper: *Treatment of pernicious anemia by a special diet.* George R. Minot, M.D., and William P. Murphy, M.D., Boston. This is the paper in the *J.A.M.A.,* August 14, 1926, which resulted in their getting the Nobel Prize along with Whipple. Murphy got the Prize, whereas Frieda didn't.

The paper (7) has a long and confused introduction on the subject of the dietary treatment of pernicious anemia. You must remember that in 1926 nutrition was just beginning to be an exact science. Minot and Murphy recognized that "The most important recent work concerning the effect of food on blood regeneration has been done by Whipple and Robscheit-Robbins and their associates." So, "Following this diet, all patients showed a prompt and distinct remission of their anemia ... except for pronounced disorders due to spinal cord degeneration."

Now I must explain my association with Whipple and why I was in Pathology. My first independent work in science was the demonstration that carbonic anhydrase is in the parietal cells. As you know, pernicious anemia is associated with atrophy of the acid-secreting part of the stomach. I was interested in acid secretion and the componets of the cells secreting acid. I very well remember the Sunday morning in Oxford when I woke up thinking that carbonic anhydrase is not only in the cells secreting acid but in the red blood cells as well. When one has pernicious anemia there are no cells secreting acid in the stomach. Is there a connection?

I don't know whether there is a connection by way of carbon anhydrase. It has never been pursued. But, as I say, I got my degree at Caltech in 1939. There weren't any jobs, and Caltech wasn't very good at getting jobs. So I wrote an abstract of my thesis and sent it to three persons I thought might be interested. One was Ajax Carlson, and I'm very pleased I didn't get a job with him. I sent it to Minot, but of course he didn't have a job for someone who was not an M.D. I sent it to Whipple, and Whipple offered me a postdoctoral fellowship, a Lilly Fellowship, at $1,800 a year. I was delighted to accept; it was a very good offer. The reason Whipple had the money was that he tested liver extracts for Eli Lilly, and Lilly gave him a sort of drawing account. I think he spent something around $300,000 in his scientific life.

Whipple was working on other things I won't talk about: the life of red blood cells, the effects of chloroform on the liver - an important topic a long time ago. Another thing he did was to turn his first idea around. He took out blood, centrifuged it, returned the red cells and kept the plasma. This is plasmaphoresis. He asked: What makes plasma proteins? He got good results, and there is a *Physiological Review* on plasma proteins by Madden and Whipple which is still worth reading (8). This was, of course, before the days of electrophoresis, the days before the exact characterization of proteins and the days before metabolic

isotopes. In addition, Whipple had a very good Department of Pathology full of persons doing good physiological research. It was a long time before I caught on to the fact that it was different from the general run of pathology departments.

Whipple had other accomplishments in academic statesmanship, but I won't talk about them. I've talked enough, and it's getting hot. My wife and I will now provide some food and drink for you. Among the things to eat will be some liver, and as you eat the liver, remember Whipple showed that liver is good for blood, and say a silent prayer for the repose of his soul.

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## CENTENNIAL CELEBRATION

As part of the Centennial Celebration of the American Physiological Society, we have invited the Smithsonian Institution to consider joining in the commemorative activities. To this end, an ad-hoc committee of interested Smithsonian Staff and the Task Force Director, was established in 1979. One of the activities now in planning will be an exhibition during 1986-87, on *A Century of American Physiology - Its Meaning to Man.* The following note is being published to stimulate the loan or gift of physiological equipment to the Smithsonian Institution to enrich the Smithsonian Institution collection.

Recently Sir John Eccles visited the National Museum of American History formerly the Museum of History and Technology to view and reminisce about the machine with which he gathered data on the function of the brain which earned him the Nobel Prize in 1963. The electrical stimulating and recording unit (ESRU) was designed and built by Jack Coombs in New Zealand for Sir John, then brought to Australia where he used it extensively, then to Chicago and on to Buffalo. From Buffalo it was sent to the museum in 1976 where it remains to be preserved for posterity. This reunion of man and machine points up the fact that the museum is collecting significant physiological apparatus or parts thereof to add to its small collection of laboratory pieces. This is a particularly propitious time to search for apparatus which played a role in unique and important experiments since the 100th anniversary of the American Physiological Society is approaching in 1987. Should any reader locate some material which appears to be a likely candidate for preservation in the National Museum please contact Dr. Audrey B. Davis, MAH 5000, Smithsonian Institution, Washington, D.C. 20560.

## SYMPOSIUM: BASIC BIOLOGY OF MUSCLES

The Society of General Physiologists will sponsor a symposium "Basic Biology of Muscles: A Comparative Approach" September 10-13, 1981 at Woods Hole, Massachusetts.

The purpose of the symposium will be to examine basic mechanisms of muscle function in a wide variety of muscle types.

Further information can be obtained from Professor Betty M. Twarog, Department of Anatomical Sciences, Health Science Center, S.U.N.Y. at Stony Brook, Stony Brook, N.Y. 11794

## MIT SUMMER COURSE

Massachusetts Institute of Technology will offer a one-week elementary course in Design and Analysis of Scientific Experiments, June 22-27, 1981. Applications will be made to the physical, chemical, biological, medical, engineering, and industrial sciences, and to experimentation in psychology and economics. The course will be taught by Professors Harold Freeman and Paul Berger. Further particulars may be obtained by writing to the Director of Summer Session, Room E-19-356, Massachusetts Institute of Technology Cambridge, Massachusetts 02139.