Remarks at Dedication of Avery Memorial Gate
Rockefeller Institute, September 29, 1965
Colin M. MacLeod, Deputy Director
Office of Science and Technology
Executive Office of the President

I'm not sure whether Dr. Avery or I had a greater dislike to talk before an audience or was more intimidated by it. On second thought I guess I'm not quite as reluctant as Fess was about "wasting people's time in listening to his thoughts" - but the difference is not great. I went through two experiences of this kind with Fess: once when he was President of the Society of American Bacteriologists and had to make the presidential address, and the second time on the occasion of the 50th anniversary of the founding of the Hoagland Laboratory at the Long Island College of Medicine, where Fess had worked with Ben White before Dr. Cole persuaded him to come to grace the Rockefeller Hospital. These were occasions when Fess made his rare public appearances to address an audience as the principal speaker.

We had a great deal of fun about his talk to the Bacteriologists, which, as Fess would say, "was a pretty good talk, if I say so myself, and I shouldn't." We talked about whether he should say that bacteriology is the "Queen of the Biological Sciences", or, as I might suggest, the Crown Princess, because she hadn't arrived yet; and so we spent the last half hour of the late afternoon, until Fess would say, "Let's go and see Do". And then a short three and a half block walk across town to see Do, who would greet us, rubbing his hands and saying with enthusiasm, "Hey, you're late, Fess, I'll make a Martini", which he would do forthwith, and when brought, would exclaim, "Fess, drink it up before the bloom goes off it!"

And so then an extraordinary hour out of many with these two wonderful gentlemen - bachelors - who knew about the goodness of life and of science and complemented each other in a way I have never seen elsewhere.

We might end up on this occasion declaring that bacteriology was not a Crown Princess or even a Cinderella, but more likely a pumpkin. But you can be sure we had a stimulating time - perhaps even blowing a few scientific bubbles, "which is all right" as Fess was wont to remark, "so long as you prick them yourself."

Fess was fond of another and related small aphorism that many of you have heard him say and which expressed his distaste for concepts that didn't lead to experiments. "Ideas are wonderful things," he would say, "the trouble

with them is that they don't work unless you do" - and he certainly worked at them, even to the final and almost uniquely painful experience for him and for us of getting them on paper in clear, economical English sentences.

I would like to tell you briefly about some of the Professor's scientific interests that antedated the studies of genetic transformation. I do so because of the threads that run through the work, and also so that the scope of his interests and range of discovery will be appreciated.

My acquaintance with Dr. Avery included only 20 years of his enormously productive scientific life. There are more than 20 years going before that I don't know at first hand - except that listening to the Professor's tales about the development of knowledge of pneumococcus and the diseases it causes, about streptococcus and its diseases, about the reaction of the body to disease, and the development of clinical investigation in its modern sense - unless reliving these experiences with him, and with Dr. Dochez, with Dr. Cole, Bill Tillett, Tommy Francis, Rebecca Lancefield and many other people, can be considered almost as good as first hand.

It is well to remember that Dr. Avery was interested primarily in disease in pneumococcal pneumonia and the bacterium that causes it, pneumococcus - and that his whole scientific life was devoted to understanding the disease, how pneumococcus is able to exert its pathogenicity, the immune responses to it, how recovery takes place and how one can intervene. Through his own work and that of the relatively small number of people who worked with him there was developed a truly remarkable body of knowledge that illuminated the way for many other fields and has had a profound influence upon all of biology and much of organic chemistry.

Let me emphasize that the Professor was interested in disease. I suspect, in our modern system of classification, that would make him an applied scientist. If that be so, let's have more applied scientists.

As we said on many an occasion, disease is as natural a phenomenon as the freedom from it. There is also the more than valid point of view that if you are going to work on the fundamental nature and reactions of a bacterial species, why not pick one that has profound significance for human welfare: why work with E. coli when you can do just as interesting things with that "lovely little bug, pneumococcus?"

The Professor had extraordinary respect, indeed almost affection, for pneumococcus and continually marvelled as to how "that little bug" could do all the things it is capable of doing.

He realized, with Dr. Cole and Dr. Dochez, before our entry into World War I, that to understand the disease process, pneumococcal or lobar pneumonia, one must have a deep understanding of the causative agent, pneumococcus. It can be said without any hesitation that the fundamental studies Dr. Avery and his colleagues carried out on pneumococcus had as their goal the understanding of the disease. The disease was the rallying point; this kept everybody's eye on the ball.

Looked at in this proper light, the picture becomes clearer and more coherent. This accounts for the progression of observations and concepts that began with the discovery of Dochez and Avery that the immunological specificity of pneumococcus is dependent on the capsular polysaccharides that cloak the cell. That the virulence of the bacterium is dependent on these capsular substances was shown shortly afterward and as a part of this demonstration, that antibodies specific for the capsule, protect against the disease. All in all a very tidy picture, and one in which few of the implications were lost.

The discovery of the role of the capsule in the immunology of pneumococcus and in pneumococcal disease was a far greater one than people now realize. Prior to this, it should be recalled, immunological specificity was safely and somewhat smugly categorized as a property unique to proteins. That any other substance could have such specificity was simply heretical and the concept was roundly denounced by some of the most prestigious bacteriologists of the day. "Contamination by protein" was the cry (and one to be echoed and re-echoed many years later when we announced that DNA was the bearer of genetic specificity - the prime mover).

The rumpus about the polysaccharides was reminiscent of the outcry about purified enzymes shortly before. Sumner at Cornell had crystallized jack bean urease and Jack Northrop at the Princeton branch of the Rockefeller Institute had isolated trypsin as a pure protein. The difference in this case, however, was that the detractors insisted that the purified proteins were not the specific catalysts but rather that some unrecognized substance present in very small amount possessed the observed catalytic activity of the highly purified protein.

These controversies weighed heavily on the Professor's mind throughout his scientific life.

The Professor was marvellously persistent, however, especially when his imagination was caught, and he persuaded Michael Heidelberger to come and work with him on the chemistry and immunology of pneumococcal polysac-

charides and their antibodies. The whole modern science of immunology stems from that association and the determination to understand the chemical basis of immunological specificity of both antigen and antibody. Michael was succeeded in Dr. Avery's laboratory by Wally Goebel who carried the work forward with imagination and devotion, as Michael himself has also to this very day.

By this time, in the late twenties and early thirties, the role of the capsular polysaccharides in the virulence of pneumococcus was thoroughly established as was also the knowledge that anticapsular antibodies protect against the experimental disease in animals and can be used therapeutically in treating the human disease. Although remarkably effective, antibody treatment was not easy to apply because protection is type specific. Moreover, in pneumonia caused by some types, especially pneumococcus type 3, with its huge, juicy, polysaccharide capsule, the therapeutic effect of antibody was simply poor.

With the firm knowledge that the capsule is necessary for virulence, the nature of the capsule well-known and methods worked out for its preparation from cultures in large amounts, a very imaginative approach to the therapy of type III pneumonia was undertaken. There was conceived the brilliant idea that an enzyme might be found in nature which could specifically hydrolyze the type 3 polysaccharide on the surface of living cells and thus render them susceptible to phagocytosis and destruction. (I should note that the main function in virulence of the capsular material of pneumococcus, the "schleimstoff", is that it is antiphagocytic. Removal by digestion, theoretically, would render the microorganism susceptible to phagocytosis and destruction.)

It was at this time that Rene Dubos joined the laboratory and brought to bear his knowledge of soil microbiology on the problem. A bacterium was isolated from bog soil, which in the presence of S III (type 3 polysaccharide) as the sole carbon source, produces adaptively, or is induced to form, an extracellular enzyme, which specifically depolymerizes S III both in growing cultures in vitro as well as in experimental infections of animals. The S III depolymerase was shown by Dubos, Francis, and their associates in the laboratory to have a remarkable protective effect in infections of experimental animals.

The enzyme was never tested in human disease because by the time knowledge had progressed to the extent that would make a clinical test feasible, chemotherapy of pneumonia by the sulfonamides had become a practical reality, which we all welcomed with gusto.

The S III enzyme story is a particularly interesting one, however, because it represents a truly rational approach to chemotherapy, based upon knowledge of the unique structure of pneumococcus which determines its virulence. In a sense, the fact that it was not applied to treat human disease is by the way, because the conception and demonstration of the principle remain intellectual triumphs.

The threads that link this story together are two, a preoccupation with the disease, lobar pneumonia, and the role of the capsular polysaccharides in infection and immunity. Many facets of these and other problems were successfully attacked by Dr. Avery and his associates over the period of some 40 years during which he was active in the laboratory.

The phenomenon of capsular transformation first reported by Griffith in England in 1928 was greeted with some skepticism on the 6th floor of the Hospital. However, Henry Dawson was able to confirm it and with Richard Sia demonstrated that, under appropriate circumstances, the phenomenon takes place in vitro -- a large step forward. A little later Lionel Alloway was able to show, although not very reproducibly, that the active substance could be separated from the whole cells and passed through a filter that holds back the bacteria. It took quite a long time after that to understand the process and to identify and characterize the active material. That story I don't intend to tell, however, because many of the points that are most interesting to me would be least interesting to you -- and there are other people who will speak this afternoon from a more important point of view, namely the impact on biology.

There are other scientific interests that I could recount such as the acute phase reaction of human and animal blood serum with the cellular or somatic "C" polysaccharide of pneumococcus. This reaction was discovered by Bill Tillett and Tommy Francis and later a good deal of work was done to understand it and to purify the reagents by the special brand of "kitchen chemistry" practiced on the 6th floor. After that good beginning, unfortunately little further progress has been made in understanding its relation to disease processes -- the "why" of it is still unknown.

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I would like to take the opportunity to show you a few pictures of the Professor, mostly taken between 1938 and 1953. Good photographs of him are uncommon, but some of these show the gentle little man in a way that published and official photographs fail to do. (Slides).

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I believe Fess would have liked this gate. He would find it hard to believe, I'm sure, and would be inclined to mock it gently in his whimsical way, "Hmm - a gate - do you suppose it's to keep 'em in or keep 'em out?"

It's good that the Rockefeller Institute has honored its most original and productive son and we are grateful to share in dedicating the "Fessgate".