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An extraordinary story of discovery: an interview with Doctor Max D Cooper

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A few weeks ago, I had the honor to sit down (in a Zoom virtual room, [figure 1](#)) to interview Dr Max D Cooper, Professor in the Department of Pathology and Laboratory Medicine at Emory University School of Medicine, eminent scholar and recipient of the Albert Lasker Basic Medical Research Award in 2019. He graciously gave us some of his time to chat about his career, to share his thoughts about the past, present and future of immunology and of medicine in general. In 2020, Dr Cooper was awarded at Emory University the renowned John F. Morgan Distinguished Faculty Lecture award, in recognition of his immense contributions in the field of medicine, pathology, immunology and so many other areas.

Octavian Ioachimescu: *Dr Cooper, thank you so much for agreeing to do this interview for the Journal of Investigative Medicine (JIM). I really think that this interview will be a major source of inspiration for many investigators, junior faculty and trainees, in a broad swath of medical fields. Allow me to jump right into it: tell us about your early training days—what led you to a career in medicine and your interest in immunology?*

Max Cooper: I grew up in Mississippi where my parents were educators—my father a mathematician and school superintendent and my mother a classroom teacher. Surrounded by books, I read a lot. Early on, I expressed a desire to become a physician. We lived in a small village so I didn't know about many occupations, but our local doctor was knowledgeable, reasonably well-off, and highly respected in the community. My father encouraged me to pursue this career path. He had wanted to be a physician himself, but grew up in a large farm family, and financial support for his education was problematic. Over time, I became more interested in sports, girls, and hunting—the usual activities in a rural community. I also realized that it would take a long time and great effort to become a physician, so my interest waned at that point. Then my wonderful older brother was killed in a car accident while on Christmas leave before his marine unit was to ship out to Korea. He left his service insurance policy in my name, which took away my excuse that financing a medical education would be problematic.

I started junior college on a football scholarship and a premed course curriculum. As a

slow quarterback—in fact, the slowest man on the team, including the coaches—it was quickly apparent that I wasn't going to make fame and fortune as an athlete. I applied for entry to medical school at the University of Mississippi, with the minimal requirement of 90 hours of undergraduate coursework, and received my acceptance while working on a summer job in a lumber mill in Oregon. At that time, the University of Mississippi med school accepted two classes each year into an accelerated year-round program, thus allowing completion of the first 2 years of medical education in 18 months. After a 1 month break, I transferred to Tulane University for the last 2 years of medical school.

For me, medical school was like landing in a fairyland. I wasn't the greatest student, but, the more I learned, the more fascinated I became with the challenges of learning about the pathophysiology of medical disorders and how one might be able to treat them. After completing medical school, I continued with a general internship in Michigan, a Pediatrics residency back at Tulane, additional training in Pediatrics at the Hospital for Sick Children in London, and then on to the University of California in San Francisco (UCSF) for fellowship training in Allergy and Immunology.

Along the way, I became interested in patients who were unusually susceptible to frequent, recurrent and very severe infections, even with common pathogens. Inherited immunodeficiency conditions were just beginning to be recognized then; for example, agammaglobulinemia characterized by an inability to make antibodies was recognized for the first time in a boy with recurrent bacterial infections by Col. Ogden Bruton, a pediatrician at Walter Reed Army Hospital. My UCSF fellowship mentor requested that, on my way to San Francisco, I learn the technique of immunofluorescence from Frank Dixon, a famous pathologist in Pittsburgh. My wife Rosalie and I had a little baby girl, not much money, and my new mentor didn't offer financial assistance to get this training.

When I presented my dilemma to colleagues in London, they suggested that I might learn this fluorescent antibody technique before leaving England from E. J. Holborough, a famous immunologist at the Canadian Red Cross Memorial Hospital in Buckinghamshire.

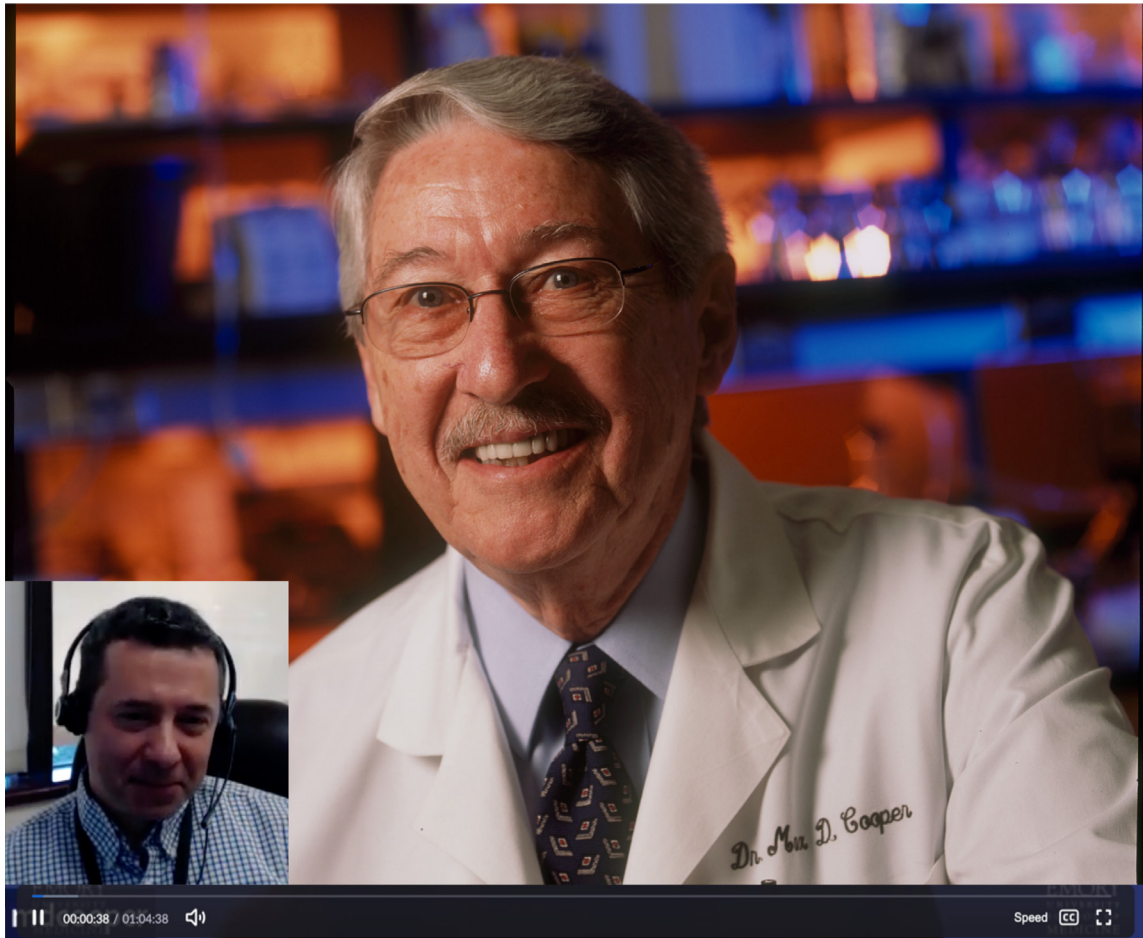


Figure 1 Dr Max D Cooper in a virtual interview with Dr Octavian C Ioachimescu.

At lunch after I arrived, Dr Holborough asked what I wished to use the immunofluorescence technique for, and I parroted a sentence from my UCSF acceptance letter, ‘to study delayed hypersensitivity in phylctenular keratoconjunctivitis’. He smiled and said, “well, that’s interesting, but as far as I know, the immunofluorescence technique is a way to study antibodies, not cellular immunity or delayed-type hypersensitivity”. I was very embarrassed by my naivety, but he said, “we have all the different steps in this procedure ongoing, from preparing an antigen, immunizing rabbits, collecting their serum, and so on. What kind of fluorescence instrument will you use?” I sheepishly replied, “I don’t know anything about the fluorescent microscopy setup”.

In the midst of my embarrassment and standing around watching people work at their lab benches, I escaped to the library to read a very dry CDC manual on using immunofluorescence to diagnose bacterial infections. Fortunately, I also found a book by Sir Frank Macfarlane Burnet, the Australian Nobel Prize laureate, on his clonal selection theory of antibody production. In reading this, I was fascinated by Burnet’s ability to present complicated immunological concepts in an interesting and understandable way. I decided at that point that even though I would always be ignorant about many things, one thing certainly going to learn was the difference between cellular and humoral immunity. This quest, which began in the early 1960s, ended up being the central theme of my entire research career.

Octavian Ioachimescu: *Perfect segue way into my next question: your impressive resume contains more than 750 articles. I wanted to zoom in on what I would call a landmark paper, the one that you wrote with Ray Peterson and Bob Good, ‘Delineation of the thymic and bursal lymphoid systems in the chicken’, published in Nature in 1965. Explain to the reader its importance.*

Max Cooper: Well, in personal terms, on returning to the Department of Pediatrics at Tulane University as an instructor, I soon realized there were two basic ways to ‘climb the academic tree’: one would be to advance through teaching and academic administrative activities, and the other was to find a way to contribute meaningful new knowledge. The latter choice meant that I needed to start all over again, so I applied to four imminent immunologists to seek experimental research training: Sir Macfarlane Burnet in Melbourne, Jonathan Uhr at NYU, Richard Smith at Florida and Bob Good at Minneapolis. All of them accepted me, with various stipulations. One of these was to bring my own salary, which was not uncommon in those days. In the end, I obtained fellowship support and joined Good’s research group in Minneapolis.

The thymus had then been shown to be important for lymphocyte development and both cell-mediated and humoral immune responses. This discovery was made around the same time by both Jacques Miller, in England, and by Good’s group in Minnesota. But well before then, a

fortuitous little-known discovery had been made by a graduate student at Ohio State, Bruce Glick, who was interested in a hindgut lymphoid organ in chickens called the bursa of Fabricius. But I feel that I'm getting into way too much detail here...

Octavian Ioachimescu: *No that's perfect, because that was in fact my next question, about your journey of discovery of the human equivalent of the bursa of Fabricius; so let's dive into it.*

Max Cooper: Bruce Glick was interested in whether the bursa was involved in sexual maturation. But when he removed the bursa of Fabricius in young chicks, this had no effect whatsoever on their sexual maturation. One of his colleagues came by later and said, "Bruce, I'm giving a course in immunology, and I'd like to demonstrate antibody production. Can you give me some of your chickens for this lab exercise?" Jaap returned later to report that "you spoiled my demonstration. Many of your birds didn't make antibodies". So, Glick and Jaap repeated the experiment to find that bursectomized birds couldn't make antibodies normally. They submitted their report to *Nature*, and received the response that, while the data were convincing, the finding was not of general significance. Their paper was ultimately published in the *Journal of Poultry Science*, which not many immunologists read. However, the report was noticed by endocrinologists in Wisconsin who were studying androgen effects on avian development. They found that testosterone treatment of chick embryos inhibited development of the bursa of Fabricius and this hormonal bursectomy severely compromised antibody production.

In other contemporaneous background studies, it had been shown that early removal of the thymus in mice prevented the induction of lymphocytic leukemias by treatment with X-irradiation or chemical carcinogens, or sex hormones, or in mice that were genetically susceptible to spontaneous leukemia development. Indeed, these findings triggered Jacques Miller's discovery of the role of the thymus in immune development. Jacques set out to find out what happened in the thymus that led to the development of leukemias and noticed that neonatally thymectomized mice were runty, lymphopenic, and highly susceptible to infections. Ray Peterson in Good's group asked whether chicks infected with an oncogenic virus (lymphoid leukosis virus) would also be affected by thymectomy or by bursectomy. With Ben Burmester, a virologist at the Michigan Regional Poultry Research Laboratory, Ray inoculated newly hatched chicks with the virus, then removed either the thymus or the bursa. Remarkably, bursectomy prevented development of leukemia, whereas thymectomy had no effect. It was unclear how this worked because the virus induced widespread tumors in the spleen, liver, and elsewhere, while the bursa itself was spared.

In my own journey of discovery, I first tried to sort out the respective immunological roles of the thymus and the bursa. When I removed the thymus or the bursa at hatching and examined the effect on development of immune functions, I couldn't reproduce some of the published results. Experiments addressing this issue in other laboratories also led to conflicting results. One suggestion was that the thymus and the bursa might have different roles in which the thymus controls skin graft rejection, the bursa controls both antibody production and delayed-type hypersensitivity, and the

bone marrow is responsible for graft-versus-host reactivity. This pairing of immune functions was discordant with the contemporaneous view of the thymus role in mammals. Moreover, the experimental findings were notably inconsistent in different strains of chickens.

During this time, we gained a different set of important clues from our immunodeficient patients, including boys with congenital agammaglobulinemia who had no plasma cells, and another X linked inherited disorder, Wiskott-Aldrich Syndrome (WAS), that was associated with severe immunodeficiency which worsened with age. Boys with WAS had recurrent ear infections, (usually bacterial in origin), eczema, and thrombocytopenia; a simple herpes simplex virus infection rapidly progressed with a fatal outcome. In examining tissues from WAS patients who died from herpes virus infection, I found severe depletion of lymphocytes in their lymph nodes and spleen. Review of their hospital records also indicated very low counts of circulating lymphocytes, despite very high gamma globulin levels. However, the prevailing idea amongst immunologists then was that a single line of cells from the thymus gave rise to both lymphocytes and plasma cells. Notably, James Gowans in England had labeled rat lymphocytes with a radioactive DNA marker which allowed him to trace their differentiation into plasma cells. His results supported the idea that thymus-derived lymphocytes could become antibody-producing plasma cells. Nevertheless, our observations in WAS patients didn't fit well with the idea of a single lineage of thymus-derived lymphocytes. There were also vigorous debates then among immunologists about whether or not antibodies themselves were responsible for cellular immune reactions like delayed-type hypersensitivity.

Even though our earlier thymectomy and bursectomy experiments were not very enlightening, chickens still seemed the best animal model to test the prevailing theories. The major problem was that, by the time chicks hatched, their immune system development was well underway. It had also become evident that the effect of neonatal thymectomy in mammalian models varied according to the length of gestation; for example, in mice with a relatively short gestational period, the effects of thymectomy at birth were more pronounced, and vice versa. This suggested that in order to really understand the function of the avian thymus and bursa of Fabricius, we needed to remove these organs while the embryos were still in the egg. This was not feasible, but irradiation offered an alternative way to turn back the immunological clock. So, after subjecting newly hatched chicks to a near lethal dose of irradiation, I removed their bursa or thymus or both (or neither), and then waited for the different treatment groups of birds to recover from irradiation, before evaluating their immune system development.

During the ensuing recovery period, some of my experimental chicks became anemic and died, so I became progressively discouraged. Bob Good reputedly said, "when is Max going to stop fooling around with those sick chicks?" Thankfully, he didn't tell this to me and Ray Peterson advised "after you carefully design an experiment, you just need to carry it through to completion; every experiment looks bad along the way, you just need to keep on to see the final outcome". I followed his advice and the results were absolutely clear: removal of the thymus plus irradiation led

to severe lymphopenia, especially of small lymphocytes, but did not prevent development of germinal centers, plasma cells, production of gamma globulin or antibodies. The effects of bursectomy and irradiation were equally clear-cut in the opposite way: these chicks developed a normal thymus, abundant lymphocytes and intact cell-mediated immunity, but they had no germinal centers, plasma cells, gamma globulin, or antibodies. These results clearly indicated two cell lineages of lymphocytes in birds and were consistent with concurrent findings in our Wiskott-Aldrich Syndrome patients.

In searching the literature, we found a report of a French family with immunodeficient members who had an atrophic thymus and lymphopenia, despite their abundance of plasma cells and immunoglobins. With these convergent sets of findings in mind, we drew the first model of dual T and B lineage development, which I presented at a pediatric research society meeting in the spring of 1965. A clinical immunologist in the audience said ‘that’s all very well and good, Dr Cooper, but chickens are not humans’. Angelo George, a pediatric endocrinologist, then rose to say, “in caring for patients with neonatal tetany due to low calcium levels because they had no parathyroid glands (the site of production for calcium regulating hormones), we found that they also had no thymus, but lots of plasma cells and gamma globulin. These findings are exactly as predicted by the hypothesis Cooper is presenting here”. Needless to say, that was a pretty dramatic moment for me.

Octavian Ioachimescu: *Great. So, fast forward—I’m going to switch gears a bit now and ask you a different question: what can you tell us about alternative adaptive immune systems in vertebrates and the biomedical potential of lamprey monoclonal antibodies?*

Max Cooper: Before the molecular biology era, our studies were heavily dependent on examining normal development of the immune system in animal models and its modification by experimentally induced and inherited immunodeficiencies. Bob Good was also very interested in phylogeny of the immune system. He and others found that even the most basal jawed vertebrates, cartilaginous fishes like sharks, have a thymus, lymphocytes, and can make antibodies; later they were also shown to have the same basic genes for immunoglobulins and T-cell receptors.

In fact, one of the first questions posed by our two lymphocyte lineage models was: if the thymus produces lymphocytes that cannot make antibodies, how do they recognize antigens? This question took about 20 years to answer. Finding both lineages and both types of immune function in the most basal jawed vertebrates drew our interest to the jawless vertebrates, lampreys, and hagfish, since they were considered to be the most basal vertebrate representatives. Jan Klein, then the head of a Max Planck Institute in Tübingen, Germany, and his colleagues had found a lamprey gene, Spi-B, that in mice is essential for normal B-cell development. By in situ hybridization, they found that a lymphocyte-like cell in a blood-forming tissue of lampreys expressed the Spi-B transcription factor. So, we began to work together to determine whether lampreys really did have a lymphocyte-based adaptive immune system. We isolated lymphocyte-like cells from hematopoietic tissues, on the basis of their light scatter characteristics, and used them to make complementary cDNA. Sequencing

of the human genome had been largely completed by then, so one could pay companies to do DNA sequencing on a small scale. We obtained several thousand cDNA sequences expressed by the lamprey lymphocyte-like cells, and then used the NCBI database to annotate our catch. We found genes for transcripts that our lymphocytes use for metabolism, migration, and so forth, but none of the cardinal elements of our immune system; that is, no T-cell receptor genes, no B-cell receptor genes, no major histocompatibility genes, no genes that were essential for assembly or rearrangement of immunoglobulin genes. This disappointing result suggested the lampreys didn’t have an adaptive immune system. Nevertheless, earlier studies had suggested that when lampreys were immunized with human red blood cells, they produced serum components which could specifically clump the donor red blood cells. However, the nature of the lamprey agglutinins could not be identified, and antibodies like ours could not be found. We repeated our search for immune system genes, and again failed to find any of the cardinal elements of our adaptive immune system in lampreys.

Before giving up, we decided to rigorously stimulate the lampreys to see if we could possibly catch lymphocyte-like cells in the act of responding. For this purpose, Zeev Pancer and I injected lamprey larvae with a mixture of live bacteria (*E. coli*), sheep erythrocytes, and two plant mitogens (phytohemagglutinin and pokeweed mitogen). After we injected lampreys with this cocktail, which a reviewer later called ‘everything but the kitchen sink’, we found expression of a lot of leucine-rich repeats. This was very disappointing since leucine-rich repeats are made by every living thing on our planet and are used for many cellular purposes. A summer student who wished to learn molecular biology techniques was assigned the exercise of sequencing these leucine-rich repeats, while we continued our search for how lampreys might recognize antigens. When Jill Ceitlin reported her sequences at the end of the summer, this was a Eureka moment because each one of them had a different sequence! This kind of diversity could account for an extensive repertoire needed for antigen-recognizing receptors. We then found they were expressed on lymphocytes, so we named them variable lymphocyte receptors (VLRs). We have since identified three major lymphocyte lineages of VLR-expressing lymphocytes: two prototypic T-cell-like lineages, $\alpha\beta$ -like and $\gamma\delta$ -like, and one B-cell-like lineage the members of which can differentiate into plasma cells that secrete their variable lymphocytes receptors. We call them VLR-A, VLR-B, and VLR-C, with VLR-B being the ones that are expressed by B-like cells. The lamprey VLR-B antibodies have several advantageous properties that make them useful for diagnostic, research and, potentially, therapeutic purposes.

We could also conclude from our studies that the basic genetic program for the T and B lineages was already present in a common ancestor of jawless and jawed vertebrates, more than 500 million years ago. The two distinct strategies for generating diverse antigen receptors represent a striking example of convergent evolution.

Octavian Ioachimescu: *Great overview, Max zooming out a little bit, in Max Cooper’s opinion, what are the three most important, more impactful discoveries in the history of immunology.*

Max Cooper: The discovery of antibodies and their ability to protect against infectious diseases was probably one of the most important. The elucidation of the protein nature of immunoglobulins, the discovery of the genes that encode for antibodies and for T-cell receptors, the discovery of major histocompatibility genes that are also essential for T-cell recognition of antigens. Last, but not least, the advent of monoclonal antibodies that are widely used as diagnostic and therapeutic agents in so many conditions.

Octavian Ioachimescu: *Tell us about the Albert Lasker Basic Medical Research Award; what does it signify in general, and for you as its 2019 awardee.*

Max Cooper: For me it had great significance because it honored the discovery of the dual nature of the adaptive immune system, the T and B lineages that we first recognized so long ago and know so much more about nowadays. That discovery changed in a dramatic way how we look at almost everything in immunology, from the realization that T cells don't make antibodies, but can still recognize antigens, and that they interact functionally with B cells. Based on this discovery, hematologic malignancies and immunodeficiency diseases could be reclassified as ones that affect either T cells, B cells, both lineages or their common progenitors, and many other things that required years and years to sort out. That early work really opened up a lot of interesting questions, so I was delighted to have it recognized.

Octavian Ioachimescu: *If you were to counsel junior or starting investigators in the field of medicine or biology, what would be your top advice for them?*

Max Cooper: Find a topic that interests you. Then find someone who's a leader in studying that problem or question. Find a mentor with whom you can interact with effectively and comfortably. And work hard.

Octavian Ioachimescu: *How about the environment? (I'm bringing Emory University now into the fold) How much does the environment play a role, beyond mentor, leader, topic, and tools?*

Max Cooper: One wouldn't have to dig very far into the field of immunology to see how important the research environment is, and that Emory University is a major contributor in this field. Just to give a few examples: The Emory Vaccine Center headed by Rafi Ahmed, the Rheumatology program in the Department of Medicine led by Inaki Sanz, the surgery transplant team spearheaded by Chris Larson and many others. Emory has enormous breadth and depth of study of the immune system, from the Department of Microbiology, Medicine, Pathology, the HIV Center, the Vaccine Center, and on and on; it doesn't end with these groups.

Octavian Ioachimescu: *Great. This is a bonus question: how can we use these advances during a COVID pandemic or in an HIV endemic?*

Max Cooper: I wish I had a good answer. As of now, the virus still dictates a lot to us. The political, economic and societal pressures that affect our response to such a devastating and adaptable virus make it an exceptionally difficult problem. One could try to find precedents among previous epidemics and pandemics, but it's hard to find one that's quite this devastating and adaptable, even HIV, influenza, tuberculosis, or malaria, although all of those are still threatening us and taking a huge toll. During the past 2 years, the development of mRNA vaccines for large-scale vaccinations in record time is just incredible. But you still have to deliver them, and if you don't inject them into enough arms quickly, the virus easily wins.

Octavian Ioachimescu: *Max, how about the Nobel Prize for medicine—any thoughts or aspirations? I pose this question because we know that more than 30% of Albert Lasker awardees go on to receive the Nobel Prize.*

Max Cooper: No. That's beyond my wildest dream.

Octavian Ioachimescu: *Well, if it is within anybody's reach, you are the only person here, in this virtual meeting today, who can get it. We will keep our fingers crossed. Dr Cooper, it has been such a pleasure, thank you so much for your time and taking us with you onto this fascinating journey.*

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