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## TRANSCRIPT - GR 05 13 22 W Kline Bolton distinguished Lectureship- "Anti-GBM Disease: 5 Decades of Progress" *Richard Glasscock, MD,MACP,FRCP,FASN, from UCLA*

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- **UVA Internal Med**

00:14:14 Okay, why don't we go ahead and get started.

- 00:14:18 I want to welcome you all to medical grand rounds and it's real privilege to introduce our inaugural don't you find old.
- 00:14:25 English lectures and brings together two titans and for allergy doctor Bolton, to which the lectureship his name and Dr Richard classic blues are often referred so I'd like to say a few words about Dr Bolton before we get started.
- 00:14:41 First Bolton really is a leading authority in rpg N and good pasture syndrome for this pioneering work doctor patient.
- 00:14:50 was the first to show that cell mediated immunity alone, without antibodies cause around the fight us it was also the first show that inter and intra molecular orbital spreading occurred during experimental gn as a day and other autoimmune diseases.
- 00:15:07 He also from a clinical standpoint disseminated the use of health mental prednisone.
- 00:15:16 So I'm really pleased that over the last two days we have recognized remarkable scientific and clinical contribution of Dr Bolton and celebrate his legacy through this distinguished lecture.
- 00:15:28 or consultant went to Washington university for his undergraduate degree and then that will score right here in Charlottesville University of Virginia.
- 00:15:36 then receive internal medicine residency training and fellowship training and Harvard This was followed by research, training at the University of Chicago.
- 00:15:45 He then returned to Charlottesville and become a faculty Member in 1973 and 1988 he became division sheet and he was division for 20 years.
- 00:15:57 He was an integral member of the have a number of national committee's practice guidelines committees who's a member of the American society of clinical investigation and he was on a number of.
- 00:16:09 panels, it was well funded throughout his career by NIH and but beyond his contributions in the field of ufology he was instrumental in establishing the Foundation and current division problems.
- 00:16:23 Through this great vision and of our medical Center they created the largest one of the largest academics dialysis programs and.
- 00:16:32 So we are really truly grateful for his incredible contributions and he recognizes our professors personal now it's been a great mentor a colleague and a friend for many years, so I like to have all the involved in DR Bolton I think he's gonna say a couple words.
- 00:17:03 So Friday the 1313, so this is filling out Bay know Robbie I promised I would sleep on in 20 minutes to that I need one is a modern.
- 00:17:18 English for establishing the lecture show really appreciate that and I have a special things for democratic my friend don't poke around much longer than even my wife.
- 00:17:31 said.
- 00:17:33 cielo contribution, because experimental and.
- 00:17:38 In one feature.

- 00:17:42requires.
- 00:17:44tends to be an education and continues to publish these won't be, as you know, speaker, I want to take this opportunity to recognize the late Dr Ben Sergio.
- 00:17:58spent many, many years as being published many, many papers who passed away, he was a true colleague and friend and collaborator and thank the people who work with the most recently in the last decade is to general.
- 00:18:14And then, finally, I want to thank my wife of 42 years Nancy my family who put up with me going to.
- 00:18:22stay in the hospital.
- 00:18:25And all those other things, trying to make up some of them are retired, but I don't think I've ever make that so thank you all again for burning, for your best so.
- 00:18:46Great well, it is my pleasure to introduce our English bibles in this reflection speaker Dr glasser for me teaching us about anti-God in business today.
- 00:18:57After graduating from the UCLA school of medicine doctor classic received his postgraduate training at UCLA Harvard and scripps research institute.
- 00:19:06over his career, he has become a preeminent we're an academic medicine and nephrology would mean interests and disease, chronic kidney disease clinical nephrology areas, among which.
- 00:19:18He has over 750.
- 00:19:21yard, is that we are pretty you'd also served as editor in chief editor for many of the leading publications, including now.
- 00:19:33Up to date apology section in the American journal property.
- 00:19:37Dr last night because previously served as president of the American society of apology national kidney Foundation and the Ad I am.
- 00:19:44He is the former Chair of the Department of medicine at the University of Kentucky and at Harvard UCLA medical Center kids received many, many awards in his career, including the David Hume memorial word of the national kidney foundation, the robber barons award of the American society.
- 00:20:01And then he had a distinguished achievement awards from the ceiling and a variety of other preeminent.
- 00:20:07Society is within an apology.
- 00:20:10he's currently Professor emeritus at the David Geffen school of medicine at UCLA and an independent medical consultant with that please join me in welcoming.
- 00:20:27introduction.
- 00:20:29Thank you all for coming this afternoon to share with us how much we care for an important member of your faculty.
- 00:20:39for mobile.
- 00:20:42Marketing gurus are called me a couple of years ago and asked me if I would kill this election, for a long time to plan for it hardly do the covert because I think we all wanted to have this personal face to face meetings are flying and of course I feel like it's a very great privilege.
- 00:21:04To be the inaugural lecture of this distinguished lecture series, because it gives me an opportunity to say thank.
- 00:21:13You a friend of long and.
- 00:21:16Not only a friend or colleague, but someone whose wife as parallel behind many professional personal words, so we have close personal connection.
- 00:21:35Now of course bottles quintessential Virgin.
- 00:21:4217 cents have as many years devoted to providing to the citizens of Virginia, the best medical care.
- 00:21:55And it's also.

- 00:21:59a wonderful division topology which now is in the hands of another extremely capable person.
- 00:22:09climb through many years of effort as on great things here and really have aeration his achievements.
- 00:22:19And this lecture and those that follow it will actually recognize his contributions.
- 00:22:28Not only to medical care, but to science to education and.
- 00:22:37Importantly.
- 00:22:41Dealers puberty.
- 00:22:44So I'm wanting to speak to you about topic.
- 00:22:49shows pretty carefully Actually, I have two topics in mind one was the biology of aging, which is something that.
- 00:22:59boldness contributed to, but in the end, I thought would be of interest to discuss a disease that bothers me great interest in anti malware base of every disease and take you through basically 120 years of history.
- 00:23:18i'm gonna try to encapsulate that in about 45 minutes, so there will be time so some of them years are going to pass by pretty quickly.
- 00:23:29 I'm going to try to provide you with an overview of this very interesting disease entity.
- 00:23:38which started out as an experimental laboratory bound up in the bedside and right now.
- 00:23:47has reached a point in this phenomena will become often cure patients from this disease and the not too distant past all the patients who acquired this disease.
- 00:24:02Are women and stage is quite an achievement.
- 00:24:07So without any further introduction let's begin this journey.
- 00:24:13I have a few disclosures for the CME.
- 00:24:18Most of these, and not all of them have nothing to do with the topic i'm going to discuss today, so they represent your interests.
- 00:24:27Those of you who are not the phone just.
- 00:24:30entitled matter based membrane disease can be defined very shortly, as an autoimmune disease to the formation of model where the bodies and or cell mediated immunity.
- 00:24:42then react with antigens present in the basement membrane of denial, I and pulmonary alveoli and cheaply, a particular engine called college and for alpha three dots invoking injury in these.
- 00:25:00For instance.
- 00:25:02let's go back 120 years of the beginning this entity was first described in experiment levels of the pasture institute 1900.
- 00:25:15series of experiments by Dr Lin and then those studies were extended in a number of laboratories throughout the world as a model of human my own reflectors usually carried out in rabbits or other small.
- 00:25:33But turning points occurred in 1967.
- 00:25:38With a description of heaven gbm disease in humans.
- 00:25:44came from the laboratory of the person shown on the right brain dead son was one of the early pioneers in the field.
- 00:25:53Of ufology and in the knowledge into the disease, so I was fortunate enough, along with other fellow with his laboratory to learn to participate in a series of studies which define this disease in human beings, as opposed to external.
- 00:26:13or very briefly go over the experiments which were done at that time.
- 00:26:19After and I collected 257 or 50 patients.
- 00:26:26Were intact others they still had their own companies and 25 who were bilateral in the fractal, which was a common procedure in those days prior to transplantation because of responding might prevent

## Unknown Speaker

00:26:41disease.

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00:26:44We talk to human basement membrane soluble is that by an enzyme and tested for somebody with a very crude test for the Roman double diffusion in general, which was not a very sensitive method, but it was only one.

- 00:27:01Time and my direct, immediate or four lessons using normal human can use sunscreen.
- 00:27:08We talked the tissues that we have available and included.
- 00:27:13In the modern g by exposing the.
- 00:27:17marijuana to low morality acid separate buffer pH three.
- 00:27:24And then we jumped us elevated material and gave it possibly two monkeys to see if we can produce seems.
- 00:27:35To have the 2323 in front of my subjects and none of the 47 patients had circulating precipitating everybody in the basement.
- 00:27:48determined by after only the fusion and the weights of 13 is too much from patients with we had in addition to gmail or disease pulmonary average and.
- 00:28:03All of which you read presenting tomorrow or Friday that linear identity deposits.
- 00:28:09worry limited and the Elliott waves when given to squirrel monkeys cause tomorrow the brightness have shown here of the lower panel is an acute sigler proliferated around the fire, so the upper panel is linear deposits, like the monkey.
- 00:28:30A showing that the passive energy alluded, on the human was capable of reproducing in the.
- 00:28:40system, the typical are for us.
- 00:28:46One particular case, I think, is some interest.
- 00:28:51In case of GL was a 29-year-old band were rapidly aggressive level and friends.
- 00:28:58With under one of my friend to me an anticipation of living related donors can they show, many are on G deposits.
- 00:29:09I n G from serum was radiolabel, given the monkeys and then down to base rate in vivo.
- 00:29:18Transplantation with the donor living related donors, we did a biopsy before implementation was negative and 75 minutes after transplantation another bomb street should linear renewal for us it's.
- 00:29:33indicating in vivo deposition of animosity, and I GG collected from the patients soon also produced the.
- 00:29:44monkeys plus fulfilling the modification of koch's postulates called whatever is possible it's an autoimmune disease.
- 00:29:56That was a turning point in the history of an eye gbm disease, because it was the first clear demonstration of autoimmune forums my own freighters man.
- 00:30:09What happened after 1967.
- 00:30:13Well, there was an early debate that occurred within a few years, so this description precipitated by a study published in the New England Journal in 1970 my rocklin Lewis and damon.
- 00:30:27who studied evidence of cell mediated immunity by individual testing using macrophage inhibition methodology and.
- 00:30:39These patients six of the 14 patient standing hand in vitro relevance of cell.
- 00:30:48or of the six patients who had surgery.
- 00:30:52biopsies and three of them have linear hydrogen deposit but one did not.

- 00:31:00 Now frank dates and my mentor person who I collaborated with the 1977 travel editorial on the signing emphasizing that the existence of cell sensitized pervasive memory.
- 00:31:19 Some situations of providers, as well as.
- 00:31:24 For the question whether there is some mediated immunity was pathogenic i'm going to come back to this comment from the.
- 00:31:36 editorial in a moment, when I discussed Dr Bones contributions feel on.
- 00:31:47 In the 1970s, of the 1980s, the.
- 00:31:51 Major development of diagnosis, was the development of sensitive amino acids are the action of small ones.
- 00:32:03 gbm anabolic well below that can be detected by.
- 00:32:08 which we use in the originals.
- 00:32:12 When the seminal observation Andrew Bolton described antibody independence and T cell dependent, I totally understand on gbm disease insurance percent demise and could not develop any be sell everybody responses.
- 00:32:35 Now, where the animals capable of developing a form of the model files that were nonlinear deposits.
- 00:32:44 They have to my own predators, and the disease can be transferred myself.
- 00:32:51 Right over.
- 00:32:54 overlapping evidence that T cell mediated hypersensitivity plays a role in the experiment.
- 00:33:04 GPM disease, this is a very important observation and tells Dr Texan that yes.
- 00:33:14 We can be sure what, at least in some forms of my own privacy so many the sensitivity can make an important impact on the development process.
- 00:33:27 Well, by 1985 or so the pathogenesis of a big element in disease had been pretty well worked out.
- 00:33:37 That was perhaps within 15 or 20 years of its original description.
- 00:33:44 The automatic body of the cell sensitization was triggered and control in part by genetic susceptibility some strains of animals, some strange and not some humans dead some humans to knock these were controlled by genetic markers.
- 00:34:02 The anti gbm bodies and circulation and perhaps the T cells so hypersensitivity T cell million understand, Germany and interact and by which Indian.
- 00:34:17 The antibodies went kaput activation and too many leukocytes reactive options and the reactive option modules were synthesize.
- 00:34:28 leaning to enter into the capillary wall by religion of the circulation leaked at the moment, space and crescents developed and i'll show you examples of this later on.
- 00:34:41 After 1985 and between 19 and now there were numerous edition of findings, we now understand the molecular nature of the basement membrane antigen.
- 00:34:55 better understand the genetic predisposition we understand the role of compliment themselves, we have very sensitive essays for the protection of managing the amount of money.
- 00:35:07 The natural history of the disease has been well described new forms of airline gbm and body, and then the linnean and perhaps most importantly.
- 00:35:18 We now have effective treatments one of those disease, namely immunosuppression classmates change, and then the next 10 or 15 minutes I'm going to review some of this information.
- 00:35:33 But, as a result of all this accumulated there, it is now possible to develop a modern classification of and I gbm the States.
- 00:35:46 There are primary forums.
- 00:35:50 Are in quotation marks because it's it's really not a very good descriptive term but it's the best we have, and these can be patients who have the Friday, as well as pulmonary hemorrhage, that is true organs are mom lung me can.

- 00:36:10 can be alone, without any pulmonary hemorrhage so called real limited the scenes.
- 00:36:16 The fibrinogen do the glomerular antibodies in which there is another autoimmune process that goes on call and I neutrophils on plasma GABA money.
- 00:36:26 And then randomly patients who have only pulmonary disease and know kidney disease often called idiopathic pulmonary hemorrhage, that is the wrong number average turnover.
- 00:36:41 Secondary forms of glomerular disease have continued to accumulate over the years, usually in case reports are small series and I indicated to you the long list of central situations in which glomerular nobody can arise secondary the some of them.
- 00:37:04 For example, patients who wonder know shockwave let the trip see for stones can develop and I glomerular disease.
- 00:37:13 Transfer transparent and patients receiving all forms of Mr lymphocytes globule which were contaminated force anti-human the basement membrane about disease and so forth, these are relatively uncommon for important to recognize.
- 00:37:33 And I glomerular nobody diseases can occur de Novo following transportation when an Oregon having responsible image and car engine.
- 00:37:45 Alpha three is present, but the recipient has never seen the other just because of a congenital hereditary absence of alpha three known as complex as.
- 00:37:58 Someone you put a normal kindling innovation with the excellent form of outward syndrome, where division and alpha three they make our body and the kidney that has been transplanted can be destroyed by de Novo GPM.
- 00:38:16 There are a number of.
- 00:38:19 Other primary funds of our fighters that for reasons we don't clearly understand getting better at it, I have no other glomerular disease members to from the lupus anger.
- 00:38:35 comes from our fighters tonight here in front of the and, finally, a new word enemy which I'll be covering briefly in a few minutes, a typical and I glomerular disease which doesn't fit in easily in any of these.
- 00:38:52 Now as I've indicated to you pulmonary hemorrhage can be an important part of the glomerular metabolic syndrome, because of the involvement of pulmonary capillaries.
- 00:39:08 it's a confusing history, because the earth's good pasture a pathologist and my wall just described the single case of failure pulmonary hemorrhage and tomorrow or Friday to send a 19 year old man during the influenza epidemic in Boston.
- 00:39:29 He wasn't studying the problem.
- 00:39:32 It was studying implementation and he happened to see this case when she reported.
- 00:39:39 Many, many years later Stedman Tang.
- 00:39:43 In a review and an observational study use the pastor's name, to coin a new single.
- 00:39:52 Mainly pulmonary hemorrhage and while we're fighters, also known as one purple with the brightness and his name good pastures name became attached to the symbol.
- 00:40:05 But only a fraction of the pensions would step in the bank really had a glomerular disease can really go back and work with the pathology from good pastures original case.
- 00:40:16 That patient has pulmonary vasculitis and splendid grand the moment it's vasculitis so almost undoubtedly patient granulomas all engines and did not have a big.
- 00:40:31 So the use of good pastures name as an evidence for this disease doesn't have a very good.
- 00:40:39 characterization from the standpoint of science.
- 00:40:43 Also, of course, patients who else pulmonary average amount of funds can have lots of different diseases, this is a nice study from the Massachusetts general hospital and.
- 00:40:55 Then part of the 1990s, showing that anti glomerular always in yellow is an uncommon cause pulmonary hemorrhage in the middle of credits.

- 00:41:10 Far more commonly is the anti neutrophils plasma everybody on new disease which cancer over that.
- 00:41:20 roughly seven times more common Jimmy mcs.
- 00:41:26 A third of the patients have no recognizable anti gbm or anger may fall into a group of other causes of the syndrome pulmonary hemorrhaging.
- 00:41:41 Here are some of the entities that have been described as causing pulmonary ambridge and the clinical syndrome of metal in front of us, but without any of the gbm antibodies are angry.
- 00:41:56 Pretty long list it's very diverse of what needs to be Captain account when you encounter a nation with pulmonary hemorrhage manifestations of blackmail pilots and know sort of logical identification of either in a gbm disease or neutrophils cytoplasm.
- 00:42:19 So the stamp maintain.
- 00:42:23 The liquid sugar the.
- 00:42:26 pastor syndrome only about 15% or so we'll have energy medium disease, whether without anger.
- 00:42:36 Over half will have anchor and only 30% will have other diseases so it's a minority position.
- 00:42:43 or.
- 00:42:44 Disease now the pulmonary average and then I gbm disease, despite plan doesn't contain any Lucas science by brockwell dealer lodge it looks more like congestive heart failure.
- 00:42:58 or the long memory and seen in mitral stenosis you do see him a server in London macrophages which are manifestations of repetitive bouts of.
- 00:43:10 pulmonary hemorrhage and deposition and iron in the macrophages and Stephen certain just iterations of typical pattern of butterfly.
- 00:43:22 infiltrates without connotation without them to learn often and the butterfly foundation, and if you do long biopsies these patients who have your regular linear deposits similar that scene in the kidney but much more vocal.
- 00:43:39 than I've seen in the kitchen.
- 00:43:43 here's an example from a male patients and to me my Fernando Fernando showing the butterfly pattern pulmonary infiltrates innovation with good pasture syndrome this case today, and he.
- 00:44:01 Is the man after when the syndrome his name earns William green pasture was a key figure in the field of ufology in the 30s 40s and 50s eventually became the dean of the Vanderbilt university school of medicine and most closely associated with that institution.
- 00:44:24 But I want to make a quotation from the biography that was written by Dr Collins, one of the faculty members and never know recalling Dr can pastors contribution, this is a direct quote.
- 00:44:39 down to good pasture personally statement in 1960 right the use of his name from the syndrome of pulmonary hypertension developer Freitas was killer property.
- 00:44:51 And he was attempting to the sermon cause of influence.
- 00:44:56 Well, the know establish any link between one kidney disease, so not too good pasture didn't think very kindly of having his name attached to the syndrome, because it didn't really reflect his interest of the time to study.
- 00:45:16 So maybe we should change the terminology and here's just one suggestion we might retain the name good pasture syndrome, but not attention to simply The anti freemium any better.
- 00:45:32 than this person who has the combination and the medical providers and commentary specifically on dealer hemorrhage on any calls.
- 00:45:42 might be called could pass through signal, and we should use the term anti gbm the scenes.
- 00:45:51 As modify this of bearings very with or without pulmonary avail or hemorrhage in this case, doing the anti gbm all around or perhaps as Dr Bolton as soon as the possibility of delayed hypersensitivity to champion.

- 00:46:15 Why is it not every patient whenever gbm disease develops how Baylor hemorrhage and told you it's not seen in all patients.
- 00:46:26 Well here's A recent study published last year of a retrospective study of over 100 patients.
- 00:46:33 all of whom have anti gbm disease and a third of them and a few sound baylor hemorrhage looking for auto antibodies to another engine within the webinar based on memory.
- 00:46:47 Not collagen alpha for collagen for alpha 3D lemon, which is the normal constituents of basic memory and very interestingly, the bound in patients who have a few cellular ambridge.
- 00:47:04 sounds with everybody's to lemon and much more common of those who do not have employees, so it may be that this difference.
- 00:47:14 Just lack of uniformity of the presentation of patients will and GPM disease is due to the presence of other auto antibodies which are not intended normally in the screening and patients.
- 00:47:32 So when.
- 00:47:34 We can define a big vm disease in its classic for us having to buy our fighters typically neck enticing and presented.
- 00:47:47 With ultra linear deposits of my GG or early iga typically IGF one some class.
- 00:47:57 granulomas are typically not seen but giant cells may, for the moment, space and complement the position is often a regular not necessarily truly living.
- 00:48:13 home scenario vm or hemorrhage can be either overt.
- 00:48:18 marcus's as acid hemorrhage or covert.
- 00:48:23 can occur very ugly somewhere between 30 and 60% of the patients and it's often precipitated by exposure to a pulmonary tops by gasoline fumes cocaine evolution and, most importantly, cigarettes.
- 00:48:42 Nearly every patient who develops pulmonary hemorrhage in the context of gbm disease as a smoker.
- 00:48:52 And if you want to stop owner average recurring reoccurring in these patients, you must don't stop smoking, or if they happen to work in the gasoline refinery and change their jobs.
- 00:49:07 that's the everybody presently have these patients with linear deposits, is of limited I GG class, I wonder if you do three typically rarely on GG for and the animal body is directed to cryptic capitals.
- 00:49:26 On certain domains of the College and for alpha three.
- 00:49:33 As I've indicated some patients can have contaminant on our body to neutrophils side of plasma.
- 00:49:41 is called anchor, and this is the combined autoimmune disease to the monster ball well.
- 00:49:51 These patients presenting to age peaks young men typically with pulmonary hemorrhage and older women, typically without valerian.
- 00:50:05 They often have iron deficiency anemia if they have pulmonary hemorrhage because the iron can be sequestered in the Center and battle.
- 00:50:16 utilization the single breath carbon monoxide the test.
- 00:50:23 is increased.
- 00:50:25 pulmonary diffusion capacity appears to be increased Well, this is through the either global in the alveoli that binds the carbon monoxide The reversal, if you have pulmonary edema and reduce blood flow to the lungs the fusion Kappa capacity, the clients so.
- 00:50:48 measurement of the diffusion capacity can often be a useful diagnostic tool to differentiate pulmonary infiltrates do one versus pulmonary infiltrates to the ordinary demon.
- 00:51:03 systemic symptoms and these patients will not have anger typically very mile rarely they can develop a typical email living room isn't wrong the blood pressures usually normal.
- 00:51:17 hypertension is typically absalom the fall into syndrome, which is massive area of the manipulative seldom occurs so patient presenting with the product syndrome and rapidly lost some kidney function is not in.



- 00:51:37The levels are normal that's a fairly rare disease occurs about one to three cases per million population, but there are more differences in the announcements, depending upon where you live.
- 00:51:52it's not an uncommon disease in China very rare in Africa and in a million other countries, and it has a seasonal distribution peaking in spring and summer.
- 00:52:05Well, this suggests the possibility of an environmental costs, specifically the violence know viruses ever been clearly identified.
- 00:52:15But coven interestingly can often does increase the risk of other gbm disease and millie epidemics and then I gbm disease have been reported in association with code and occasionally with enjoying.
- 00:52:36This is the example of the clustering of diseases in certain regions, this happens to be Ireland the red indicates extremely high prevalence.
- 00:52:49The white yellow very low problems so from the northern part of Ireland to the southern part of our there's a marked difference in the incidence of.
- 00:52:59disease we don't know why this happens, but it is a common phenomenon.
- 00:53:07Now the pathology and then the analogy of an amiable pathology gbm disease on over fairly quickly.
- 00:53:16This is what it.
- 00:53:19looks like when you develop a gbm disease moment space.
- 00:53:25is full of cells.
- 00:53:30obliterating moment space, the capillaries are shrunken and compressed.
- 00:53:38One of those Nazi paranoid and across the stereo.
- 00:53:43and one wonders when the woman spaces so for themselves, like this, how the urine could never reach the proximal to build.
- 00:53:51And then back so much think justin that the requirement kidney function invasions is due to a form of obstructing your office in which the obstruction as location within mobile in space preventing any passage and buren into the box new to me.
- 00:54:13The questions in these patients is almost always have the same age infant treating this disease is a bronzer affects the majority of the population and then stops.
- 00:54:28Whereas other diseases, the age of the lesion the kidney varies widely.
- 00:54:38Of the electron microscopic level and in the middle for us level the typical many.
- 00:54:45A little for us, and so I GG typically I want to see our energy do scanning electron microscopy you can see perforation.
- 00:54:56Of the camp world was sort of one unit to have a car exploding pumping because of pressure and weakening of the capillary wall from enzymatic digestion you find these.
- 00:55:10These holes allowing fight religion, the leak in the moment space, a large molecule or another Gospel memorization helps to cause the progress of inflammatory cells and the proliferation of our partner sites and vessel epithelial cells forming.
- 00:55:31yeah other bodies inside Center typically energy one.
- 00:55:36They can follow.
- 00:55:40Many years after having low grade anger.
- 00:55:46In other words, there is a program of anti gbm disease that cannot be recognized from employee only store logically.
- 00:55:55And then, this manifested by load titers of this empire neutrophils side of was began a body and then for reasons we don't understand there is a burst.
- 00:56:06of an antibody production resolving and destruction of the capillary will Lawson can be function, and then the body will go away.

- 00:56:16 So it tends to be a self limiting disease, fortunately, we have antibody measurements that can quantify, the gbm body in the circulation typically these are enzyme test, but there are others, including Western blot.
- 00:56:34 These tests are highly specific and quite sensitive 95% sensitive 95 to 99% specific but false negatives to curve.
- 00:56:49 native test doesn't completely exclude the possibility of the.

### Unknown Speaker

00:56:54 gbm disease.

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00:56:56 it's an abrupt onset of disease and even without any therapy the antibody levels will decline spontaneously, but of course if you've already damaged over now bronze don't come.

- 00:57:10 So you can have permanent was some kidney function, even as the antibody levels disappeared, however, with adequate treatment with aggressive treatment.
- 00:57:22 steroids cycle falsified and plasma exchange they had about the levels, the client quickly usually or negative, within a few weeks, a few months.
- 00:57:35 relapses of the animal body are very uncommon and this self-limited nature of the seeds is very important, because it means if you treat the disease before the reversible damages incurred these patients may now opportunity to have children of their scenes.
- 00:57:58 here's what happens to the antibody levels, when you do plasma exchange on the left.
- 00:58:05 His patients who were treated appropriately with full dose files much change very few patients and antibody levels detectable.
- 00:58:15 More than about eight weeks, this is the log scale if you didn't get enough plasma change the antibody levels persistent.
- 00:58:23 and have your untreated antibody levels of could persist in many patients, for as long as 40 weeks so self-loving the nature doesn't mean that it goes away in a matter of weeks or days it may take a more prolonged period of time.
- 00:58:42 Now i'm not going to spend a lot of time on Anna gbm disease with ankle.
- 00:58:49 Insurance you recognize that it is fairly common one in the 14% in seeing more often and older patients that are younger patients, and when you have a gbm antibody combined with anchor on the prognosis there's a lot worse if you have a QA alone.
- 00:59:10 About half of the patients who have anka gbm disease pulmonary hemorrhage about similar to those who have a chimney.
- 00:59:22 Now we know a lot about the album body itself and the energy and part.
- 00:59:29 Without any evidence of the base of memory i'm only going to focus on to college and for alpha 345 which was one of the major constituents in the basement membrane in lamb, which I mentioned earlier, in the context of severe pulmonary hemorrhage.
- 00:59:50 This is a bag dramatic sketch from ability Hudson's beautiful work showing where this energy and is located and send the deck summer of the non collections domain.
- 01:00:06 of time for college and which is this triple helix and the 345 antigen of the Alpha chain of forms this globular non.
- 01:00:19 color collection this domain that's not triple helix domain matters for the engine is working, whether it's encrypted.
- 01:00:29 isn't exposed under normal conditions, the antigen is all the inside of the excellent.

- 01:00:38The heck summer is maintained in and swamp cooler shape and the configuration by a series of what are called SOFA looming SOFA little me bonds different than most bands there Brahman they are Roman sensitive and when these bonds are broken, we have summer.
- 01:01:02break and exposes the cryptic evidence.
- 01:01:07So when you have a gbm body, disease and the antibody binds It means that the X uber has been the society.
- 01:01:18Which means that the SOFA normal ones, have been broken.
- 01:01:23How they are brokers and question have some interest because the accelerator space, in fact, even if you add everybody in the circulation in Canada.
- 01:01:34Well there's a very interesting proposal has been made by doctors McCall which is from Dr Johnson's laboratory and by Lucy from Emerson that an antibody to an enzyme responsible for forming these bonds per oxidation allows the SOFA millimeter bonds to disintegrate.
- 01:02:04And therefore, allowing the extrovert to become unstable and binding the animal so it's possible that this hypothesis demands that patients will then I gbm disease.
- 01:02:19Have preceding autoantibodies to procrastination that inhibits the ability, the enzyme to maintain the stable configuration of the APP server that's exposing the cryptic.
- 01:02:38Now, Dr openness been several contributions in the survey, because he was one of the first to delineate the nature of the linear time which must contain one amino acid disparaging in order to become an active in the dominant capital.
- 01:02:57And he also was the first to demonstrate that there is spreading of the animosity from one end to another only in the same molecule possibly other.
- 01:03:10There are two major help adults and cryptic.
- 01:03:15alpha 345 excellent up and talk a and don't be very interestingly those patients make our body boss leads we have very severe can intercedes much more severe than patients to make everybody only interviewed.
- 01:03:37about an acre dependencies on protein sources that are released from active in political science is probably a science probably is.
- 01:03:47made I just the basement membrane and therefore can thereby release these cryptic capitalists and that may be another explanation for the connection between ni gbm disease and anger.
- 01:04:02When you can detect these antibodies fairly regularly by a number of approaches the one most commonly used as an advisor say involving recombinant humans college now for our challenge and for alpha three.
- 01:04:22Capital that's the untapped molecules not the linear peptide reaches the immuno dominant.
- 01:04:30contains the whole summer.
- 01:04:36Now some patients who have linear deposits of ign their kidney have no detectable everybody in the circulation, for instance.
- 01:04:46Well there's a lot of different calls to seven servings serves mainly as an entry point into an enemy, that I think many of you may have encountered or discussed.
- 01:04:59That is a typical when time gbm disease have been which patients who have linear deposits in there can be of no detectable and above in different significantly from the classical form the other reason for antibody negative and our champion disease is that conventional.
- 01:05:24of Illinois acid is the alexa may not be uniformly sense for the action of these antibodies and then patients with antibody negative and I jvm disease, with the eliza asking when you test the syrah again using indirect incidental fluorescence as the as a method you can frequently.
- 01:05:46housed in anatomy bodies, and this is a way to uncover amassed.
- 01:05:55A typical add on gbm disease is a very strange at.
- 01:06:01All is found in.
- 01:06:05Patients averaging about 50 they never have pulmonary hemorrhage.

- 01:06:10 They have the body syndrome commonly.
- 01:06:14 They have mother deposits of mine GG which never happens in classic.
- 01:06:22 gbm and they don't have crescents or they have crossed and story cell phone and it's a slow evolving disease, it does not produce rapidly progressing.
- 01:06:37 Now I'm only going to say a few words about genetic susceptibility and leave about four minutes or the management.
- 01:06:47 Or the rest genetic susceptibility here on the Hla illegals that are assumption with high risk.
- 01:06:57 and low risk about 80% of patients who have classic and I gbm disease will have the Hla Dr to Hla Dr P 115.
- 01:07:11 So there is a distinct measurable genetic predisposition to this disease, you wonder impatience carrying these illegals shouldn't consciously avoided.
- 01:07:23 Exposure to hydrocarbons, how occupations and gasoline refineries because they might be additional resource partners folder in which we don't know the LG.
- 01:07:35 GPM disease we suspect that it has an environmental origin because of the geospatial and seasonal distribution, but we really don't know.
- 01:07:47 Now that he has changed dramatically.
- 01:07:52 largely because of the discovery of my lock, one of the hammers hospital, many years ago of the efficacy of plasma exchange the physical room everybody from the CERT delish by exchanging plans.
- 01:08:08 Seven patients are treated Bible commentary hemorrhage and same time, all of whom had a gbm disease.
- 01:08:17 And then were treated either daily or every other day, with a whole plasma volume.
- 01:08:24 Three years ago, and your patients fully recovered from this treatment for injury patients never.
- 01:08:34 So there was a good indicator of responsiveness and all patients all five patients with pulmonary image dramatically improved pulmonary and.
- 01:08:50 So this evolved the standard tree when I gbm disease, called the Hammersmith protocol is pregnant alone and the high doses initially.
- 01:09:03 Using the Bolton protocol.
- 01:09:07 intravenous.
- 01:09:09 On oral.
- 01:09:12 Oral cyclophosphamide not intervene and.
- 01:09:16 Oral cyclophosphamide and reduce those in the elderly or patients with severe renal failure and plasma exchange, they would one plasma volume minimum.
- 01:09:29 Using either albumin or fresh frozen plasma placement fluid and when you do that here's the outcome, based on what the service graph need is.
- 01:09:40 At the time, patient start treatment, and this is the five to 25 year survival rate I'm to 25 years, not just be here for a long while, if the same crap he knows less than 500 micrograms per liter around 5.7 milligrams per deciliter.
- 01:10:02 Patient and getting survival it's pretty good at 4% 74% so a little less if you have committed grabbing above that that you have on dialysis but a few requires dialysis treatment.
- 01:10:20 of success anything form of treatment rapidly the clients in this case, kidney survival felt 5%.
- 01:10:29 After five to 10 years.
- 01:10:33 larger series done in other countries have again shown that this level of service grappling around 5.6 5.7 is a marker of response was when you change their good response.
- 01:10:53 If you treat the patient early, therefore, it is very important that the diagnosis of this condition being made and treatments started as soon as possible on the weekend, necessary and often starting treatment, based on clinical.

- 01:11:13 diagnosis, rather than having a confirm tissue diagnosis, because days.
- 01:11:21 The outcome of these patients can be predicted fairly accurately by both the Serb cramping was at the time treatment was started, this is a very large series over many decades from China and showing that certain crafting remains the best predictor of outcome long term and short term.
- 01:11:43 Now rather features like calling when the area like the number of gmail either involved with crescents and perhaps the tighter event I gbm but as been stressed pipeline and others tighter amanda gbm is known as predicted that she would.
- 01:12:01 relax relapses and recurrence of the disease are rare in.
- 01:12:07 Other silently uncommon and the disease and not to recur in kidney transplants, if you wait until the antibody levels disappeared that's about six months.
- 01:12:21 There are many forms of therapy, other than the hamsters borgo I don't have time to do them individually, but I would like to focus on to.
- 01:12:32 Thompson man as a substitute for cyclophosphamide no control trials, but evidence suggests that returns, a man a scene in 20 monoclonal antibody can substitute for cyclophosphamide if you have a patient and you don't think.
- 01:12:52 is a good idea that may be particularly useful for the rare patients relapse.
- 01:13:00 Perhaps.
- 01:13:01 The most interesting is the last one I will show on.
- 01:13:07 gbm disease, and that is the use of an enzyme to ride from strap the COPs on that please I n G in the circulation and they get no longer capable of functioning as an animal.
- 01:13:25 This is called invalid for days that's the generic term for it in a paper published last week and Jason 13 subjects with gbm disease received one intravenous infusion of this compound Point two five milligrams per kilogram and their prognosis was powered.
- 01:13:50 The android GPS levels in these patients fell to contactable measures within two hours of the infusion, it is the most rapid way of reducing gbm everybody's you know even faster plasma.
- 01:14:10 Unfortunately, the effect is not lasting, there is a rebound starting in about three days, but it gives you three additional days.
- 01:14:20 whereby other treatments, can be a sign of awesome on steroids and placement change here's the outcome in this pulmonary pilots.
- 01:14:31 15 patients 10 on the outside now on dialysis of the patients who are on dialysis at the time they got the infusion final game of diagnosis 15%.
- 01:14:46 Remember the store and controls or somewhere about it to a person with plants will change this pilot study is now being expanded into randomized control trial, hopefully, leading to the approval of this drug or the treatment of a gbm disease as a supplement to play as much.
- 01:15:09 So.
- 01:15:12 A lot of things have happened in the 55 years since our gbm disease was described in humans hundred and 20 years since the experimental on.
- 01:15:26 And it is now probably the best understood the bowel disease, and we can be, and perhaps even.
- 01:15:38 We know it's pathogenesis we know the genetic susceptibility we know the targets we know the other one we know the cellular vectors we know it's behavior in normal snatchers good prognostic biomarkers and, most importantly, we have treatment if you recognize these patients early enough.
- 01:16:01 Earlier, and you instant too aggressive therapy, you can cure this disease.
- 01:16:10 Unfortunately, a lot of patients don't get lunches in time.
- 01:16:15 that's not the following positions it's the fall of the recognition this disease as early as possible.
- 01:16:23 Well, I want to thank you all for your patience I'm sorry I went over a minute or two I didn't want to recognize my deep affection.

- 01:16:34Or the person over when there's this lecture them on this lecture final and I hope subsequent lectures will even further and Bella wonderful reputation of the spine man and very responsible and dedicated citizen of Virginia, thank you very much.
- 01:17:10properly.
- 01:17:29And then, also for folks on zoom feel free to send messages on the chat I really enjoy your.
- 01:17:36Memories from my thesis you know, probably was struggling.
- 01:17:47When.
- 01:17:56It was published.
- 01:17:59and
- 01:18:02And the second.
- 01:18:05Time.
- 01:18:10In.
- 01:18:19In a person's studies in jaipur.
- 01:18:25And the focus on.
- 01:18:27Being mostly on anymore and I'm wondering whether we should add something like you know get a text he says.
- 01:18:39He says, especially in those instances where there is no, no, no energy.
- 01:18:48And and end up on this let's not sure you're also possible to find bone and I certainly would like to have an answer.
- 01:19:01We do know that with patients, we have linear deposits and web circulating gbm about instead of you administer steroids, which.
- 01:19:13Of these notes and you would Minister cyclophosphamide which has its predominant but on the cells may also know some.
- 01:19:22of US plasma exchange, you can invite greatly modify the natural history of this disease now once we use cycle sparring or any final blog and we don't know.
- 01:19:38But we do have on one and positive one and move their body structure of the body of evidence.
- 01:19:50Can dramatically affect the course.
- 01:19:53While.
- 01:19:56Learning data was very good Thank you.
- 01:20:01We do.
- 01:20:07Jesus, and he said the insertion.
- 01:20:12Order, the process that we do will decrease production because we're actually, then we can T cells as well Jesus basis.
- 01:20:25To them right.
- 01:20:26And those.
- 01:20:29are very effective it.
- 01:20:34Is and studies are saying that providers in a lot.
- 01:20:43More.
- 01:20:47immune system.
- 01:20:50And the goal is either every day is hating it early and then control this was important from a disease.
- 01:21:00I should stress of by then at the top, that is recognized as a T shirt.
- 01:21:08T cells are the first cells to recognize the pattern genetic capital subsequently those T cells cooperate with B cells to produce antibodies.
- 01:21:21So the question is, what is the vector of the familiar recent memory damage.
- 01:21:30there's no question in my mind that the cell activation is involved in our body that's pretty clear question is.

- 01:21:39 How much to what extent you sensitize T cells, result in damage in the chicken model, Dr, the answer is an equivalent you don't need the body, the damage basement membrane T cells are sufficient.
- 01:22:01 Can I say the same thing about human disease probably not because it's extraordinarily difficult to do the kinds of experiments that find them and chickens in humans.
- 01:22:14 I can't percent demise a human.
- 01:22:18 The only thing I can do with me because protons a gamma bomb Libya.
- 01:22:24 and expose the patient database in memory and see if they developed energy becomes is I'm not going to do that, so the experiments that you can do in humans are limited in their ability to demonstrate as Dr Bolton dead in the chicken and crucial role T cells in the damage.
- 01:22:50 Great thanks very much I wondered it's interesting to me when you look into shooting a piece that it seems likely to choose to him he's always you're talking about so it a women who represent the later people enter is there to him.
- 01:23:08 genesis telescopes are getting both ends at the same time that we think is happening to the T cell and anka media T cell and then he starts.
- 01:23:19 happening at the same time well the michelle's the director of our different B cells to make an agenda to sell clothes right there.
- 01:23:30 Having perhaps at the same time.
- 01:23:34 The question is what comes first.
- 01:23:37 Is an ni GPM disease destroying the lizard brain leading to some kind of.
- 01:23:45 autoimmunity leukocytes or as a.
- 01:23:49 Body leukocytes predisposed to establish the best memory seems to be more turn on the light of the fact that, if you take Sarah from patients who have and I gbm seeds that have stored Cyril months or even years before they did Alabama GPM disease, they have detected boring.
- 01:24:13 This means to me that there is something about anchor maybe its ability to cause the fact in proximity is inch allows innovation, the.
- 01:24:26 Excellent to break apart that contributes to the stability to energy, I think that's more likely than the reverse, and I have seen I'm taking care of patients who are angry disease and years later, they developed a due.
- 01:24:49 To the reverse doesn't seem to happen nearly dissolved.
- 01:25:03 One thing in terms of.
- 01:25:06 early treatment, and that is the Chinese are doing the.
- 01:25:13 Show ebooks brain occurs GB and disease and those patients that were caught early again have a question on there, everybody, everything is vision in my head.
- 01:25:27 I think what will knock your boldness emphasizing is very true, and particularly when.
- 01:25:36 The epidural spreading does not occur that happened to be.
- 01:25:42 Chinese patients who have little animal body their photography have a very good.
- 01:25:47 Chinese patients who have higher body being very poor prognosis now our testing methods.
- 01:25:56 will choose the whole episode.
- 01:25:59 comprise to both A and B cannot differentiate so when you do a lab test and you get a report license.
- 01:26:07 And I GPM antibodies 110 units you don't know how much of that is directed that happen to be or happen to pay or the combination of the two.
- 01:26:17 This is why animal the levels may not have as much prognostic utility because they don't give you the full spectrum of information, how much of a dope spreading has occurred in order to do that, you have to do a doctor.
- 01:26:32 login synthetic peptides that represent all of the different array of episodes on the exit our margin.

- 01:26:43 And as I've shown you in lemon, which is a completely different molecules if you ever talk spread to melanin now nobody should get Boehner and.
- 01:26:55 So at the top spreading inter.
- 01:26:59 and intra molecular spreading probably as an important aspect to the natural history, which is something that you said I think my.
- 01:27:14 answer is accountable for the students in the residence here we've got an appointment, using a sophisticated recombinant protein, for he.
- 01:27:25 says the old fashioned interrupt me know versus if he has many benefits, because there are some cases that nobody gets it off before and I can see all three with regular caloric additional leisure.
- 01:27:43 or anything else, unless you do an interview questions so you think that you have something else going on the.
- 01:27:54 old version so.
- 01:27:57 If you have a patient was Pacific or male or product is rapidly progressive disease.
- 01:28:03 And you do a Bob seaman shows linear for lessons and you do an energy, the amount of money that's begun with a real common human and you should always do indirect in you know, for us, because that will take us all empty or.
- 01:28:23 Rather than all the other energies that are in based memory culture of employing substrate and expenses all.
- 01:28:32 And I think there's a very important point and it's often missed because they sent me how can I do plasma exchange and the patient without anybody in their circulation well how do you know that they don't have them.
- 01:28:45 You depend entirely on a single test and then we'll try.
- 01:28:51 Alright well.
- 01:28:55 I hope the next speaker comes keeps on time but.
- 01:29:02 The best job I can possibly do.
- 01:29:05 To.
- 01:29:16 Thank you for this event, this is a wonderful