JOHN HESS: Good afternoon and thank you for coming. This is a presentation that I put together specifically at the request of Eileen and Bryce Robinson. They had called me up and said, when are we going to put TEGs in the laboratory, and I said, why do you want them? And they said, well everybody's using them and we'd like to be part of that and we want them. And I said, no you don't.

[LAUGHTER]

Let me point out that I have several conflicts of interest here. I have two US patents related to hemorrhage control systems, bandaging, and things like that. I receive the writer's share from UpToDate for the section on massive transfusion. And until I came here I was the technical officer on a Navy SBIR to build the next generation of TEG machines. We had a half million dollar contract. And it's out of these experiences that I want to talk.

But first, let's start with a case report. You remember the mudslide at Oso, now two years ago. And this is the critical patient, the 5 and 1/2 month old infant who was evacuated here to Harborview and showed up in our emergency room with a hematocrit of 11, a INR of about 2.7, a fibrinogen of 50. And you will see that we did a very nice job of resuscitating that infant using our standard techniques of measuring with an emergency hemorrhage panel, which we had back within 15 minutes of the child's arrival. And the platelet count at the time the child was admitted was 200--

I'm sorry, was--

Was 300,000 and nobody thought that was a problem.

The initial head CT shows the critical injury. The child had a fractured skull, has edema there in the occipital portion, and a large scalp laceration that was the site of all of the bleeding.

What you will notice is that the child's platelet count fell over the next several hours. From the 300,000 on admission to 122,000 at a time when we had corrected the problems with plasma coagulation. The repeat CT scan now shows bleeding intracranially. And despite this obvious evidence the child is bleeding, and it's probably related to the platelets, because the platelet count was 122,000 nobody did anything about it.

Until 12 hours later when the platelet count had drifted down to 88,000. This is a clear example of treating the number and not the patient. And, you know, what I want to talk about is the integration of numbers and patient care into thinking critically about what we're doing when we're treating trauma patients.

So I want to talk about the coagulation system, and how it works, and why it fails in trauma. I want to talk about the role of the emergency hemorrhage panel that we have here at Harborview and that is our mainstay in trauma. care. I want to talk about how TEG works, and how to read it, and why TEG gives little information that's useful in trauma patients.

First, let me start by saying that the human coagulation system is slow and weak. Cut yourself and it takes five minutes to stop bleeding. But in a trauma patient you can bleed to death in five minutes, you know. It's a problem of scale.

And the material that you have in your coagulation system is limited. If you think about it, you've got 10 grams of fibrinogen, two teaspoons, you know, circulating in your whole body. 300 milligrams per deciliter times about 30 deciliter of plasma. You've got 15 ml of platelets, again three teaspoons, but one's in your spleen, you know. So you've really got two teaspoons of fibrinogen and two teaspoons of platelets to try and deal with serious injury. But 40% of that may be on the floor by the time you arrive.

And yet 10 times more people die of clotting than die of bleeding. Heart attacks and strokes are the most common cause of death in the United States. And clotting is a continuous risk. Massive bleeding is a rare event. You know, the clotting system has evolved over half a million years to be balanced to the risks of life.

Remember what hemostasis is. You form a primary platelet plug. You then overlay it with a fibrin clot. That clot contracts. And you have parts of it that limit fibrinolysis.

So let's start with platelets. Platelets circulate as small plates. They're about three microns in diameter, about a micron thick. When they activate they put out pseudopodia and go through a whole activation process. In cartoon form, here is that process demonstrated.

And remember, we talk about platelets adhering, activating, secreting, and aggregating. They adhere because as they pass over collagen membranes, Von Willebrand's factor bridges from type-III collagen to the glyco-protein 1b-IX receptor. Physical traction on that receptor activates platelets. When platelets activate they send out a calcium signal and they racemize their membranes. Phosphatidylserine and other negatively-charged phospholipids that are usually on the inside end up on the outside.

They secrete. You know, they secrete the contents of their alpha granules, which are typically proteins, things like fibrinogen, factor V, Von Willebrand's factor. Things that would be nice to have if you're trying to build a clot released in high concentrations in the local area. And their dense granules do the same thing, secreting ADP and calcium, mid-chain polyphosphates for the activation of factor XI, serotonin, and other small molecule mediators.

And the activation of the membrane causes the integrons on the surface of platelets to go from the resting to the open state and become active binding sites. You know, for adhesion molecules. And specifically, the 1a, 2a integron opens and binds firmly to the collagen in the base substance. The 2b, 3a integron opens and becomes a binding site for fibrinogen. One integron will bind one end of a fibrinogen molecule, another platelet that will bind the other end, and that's how platelets aggregate.

So in another cartoon here we can see inactive platelets circulating or walking along the membrane, doing membrane surveillance. And when they come to a place where there isn't an endothelial cell, where the ground substance has been exposed Von Willebrand's factor will bring to that collagen and the platelet will find that and bind and activate. And then when they activate they open their integrons and secrete.

Another cartoon showing essentially the same thing. An inactivated platelet comes on a place where platelets are bound and secreting, and gets chemically turned on to open its integron and allows them to aggregate to form platelet clusters.

One more cartoon. Here you see platelets, Von Willebrand's factor, and fibrinogen circulating over an intact endothelial. When it finds a break in the endothelium Von Willebrand's factor binds the platelets. The platelets activate and form a primary platelet plug, which then gets overlaid with secondary hemostasis, you know, fibrinigin clot.

Red cells are an important participant in this, in the sense that they're heavy and they push the platelets to the edge of the circulation increasing their local concentration. Here at a hematocrit of 40 and a normal platelet count you see large platelet aggregates forming at the site on a collagen. And this is done in a flow chamber, you know, and then the flow chamber is sectioned and stained and presented here.

When the hematocrit drops and the platelet count stays the same you still have much smaller aggregates. And finally, you know when the hematocrit is low and the platelet count is low you have very small platelet aggregates indeed. And the problem as you know as doctors is, that this is where heart attacks occur, at a normal hematocrit and a normal platelet count, and you form big, healthy clots. And this is where trauma occurs, at a hematocrit of 20 and a platelet count of 50,000, and you can't get your patients to stop bleeding.

OK, so there are two roles of platelets in hemostasis. One, they form these primary plugs. And two, they activate their membranes to support the coagulation system.

Now, most of you were taught that this is what the coagulation system looks like. I certainly was. You know, Earl Davie here, the University of Washington, described it in the classic article in '64. And I basically got to sit in the front row at first year lectures in '67 and listen to him talk about it.

What they did is, they found hemophiliacs who had different kinds of hemophilia. You know, so that they could-- when they found a new hemophilia they would mix him with blood from all the others, do a mixing study, and if they found somebody who got better with everybody else's it was a new hemophilia. They could take that patient's plasma and by chromatographic methods keep isolating more and more fragments of it until they got down to the protein that was missing that corrected his problem. Or hers.

OK, if you think about this limited proteolysis cascade model, it can't possibly explain coagulation. You know, this is what happens in the test tube. It's not what's happening in the body. The kinetics can't possibly work right.

We now know that it's the extrinsic system that really is the driver for coagulation. And that is driven by tissue factor and factor VII. Factor VII is produced in the liver. It auto-activates in the circulation to a limited extent, and more so when bound to tissue factor.

And tissue factor exists on every cell in the body except endothelial cells and blood cells. So any time you have a break in the endothelium you are exposing tissue factor.

The factor VII has a very short half life. It's a small molecule. If it diffuses outside the body it binds to tissue factors internalized and broken down. Only when it's exposed to the break in endothelium do you get it exposed to other plasma factors where it's enzyme activity turns out to be activated.

Normally, there are about 5,000 molecules of tissue factor on every smooth muscle cell and fibroblast in the sub-endothelium. And when you expose those molecules-- you know, which is to-- these tissue factors are floating low in the membrane in these unactivated membranes because the negatively charged phospholipids are pumped to the inside of the cell. When the cell is activated it will scramble these phospholipids and the tissue factor will come apart and move up higher, and bind to the exposed factor VII that it meets when it sees fresh plasma.

And that factor VII then is stretched between this membrane where its vitamin K dependent factors bind to those negatively charged phospholipids, pull that tail out, open the molecule up, so it can be a fully active enzyme. And as clotting factor it then activates factors IX and X.

As these phospholipids are normally pumped to the inside by aminophospholipid translocase flippase, when the cell is activated by that calcium signal flippase becomes floppase and flips these negatively charged phospholipids onto the surface. Where you'd think, for charge reasons, they'd spread apart, but for Gibbs free energy reasons, they stack and form small negatively charged phospholipid rafts which attract calcium. And then, the vitamin K dependent dicarboxylic acid tails of the vitamin K and calcium dependent clotting factors bind to them. As do their co-factors.

And on this structure a negatively charged phospholipid raft with a clotting factor and a co-factor, the clotting enzymes are 10,000 to a million times more active than they are free in the plasma. That's where the amplification of the clotting system comes. It's also what localizes it precisely to the site of injury.

There are three sets of these clotting factor complexes on smooth muscle, and fibroblasts, and other somatic cells. Tissue factor binds factor VII and activates IX and X. On activated platelets factor IX meets up with it's co-factor, factor VIII, and activates X. Now, you can go straight from making X here to making X binding with its co-factor V, and making thrombin. But we in fact know that the system goes the long way around because missing factor VIII or factor IX, hemophilias A and B, are diseases.

And so it efficiently works this way and efficiently can be driven this way with high doses of factor VII. Which is why we use high doses of factor VII to treat hemophilia kids with inhibitors.

So our modern sense of how the coagulation system works was really proposed by Maureane Hoffman. You know, that this initiation phase occurs on the surfaces of macrophages, in which tissue factor makes a little bit of X, which makes a little bit of thrombin, which activates some extra factors, but is probably destroyed the X and the thrombin by anti-thrombin. But IX is relatively protected from anti-thrombin, finds its way to the surface of the activated platelet where IX and VIII make more X in large volumes and drive a thrombin burst, which will then make more of these co-factors activated and make fibrin, make factor XIII for cross-linking fibrin, and make the thrombin activated fibrinolysis factor for limiting fibrinolysis.

And so kinetically, we've come to understand that the clotting system is really a 7, 10, 2, 1 extrinsic system. And what we used to think of as the extrinsic clotting system is largely a set of feedback loops. That 11, 8, and 5, all activated by 2, feed back in and make each of these steps work much better, help localize clotting, and help drive it so that we get a massive thrombin burst highly localized to the site of injury.

This is what a clot looks like. You know, there are relatively few platelets there, There's a lot of thrombin, a lot of fibrin. And the platelets pull that network together. And that's actually what we measure as clot retraction.

Now, as I mentioned, this is the kind of injury that it's hard to imagine how two teaspoons of platelets and two teaspoons of fibrinogen allow you to control.

And lots of other things are going on when patients are injured. We start with those 10 grams of fibrinogen and 10 ml of platelets, but there's loss. We end up diluting them with fluids, the body dilutes them as hypotension leads to drawing of fluids into the intravascular space because the blood pressure is no longer opposing the oncotic activity, and water moves in and dilutes all of the proteins. Hypothermia and acidosis impinge on the clotting system. And classic DIC consumption and fibrinolysis is going on.

Again, loss. You start with 10 grams of fibrinogen and 15 ml of platelets and 40% of it's on the floor before you start.

Temperature. You know, Greg Jurkovich wrote the classic paper that if you--

Have a massive injury and a core temperature of less than 32 degrees, you do not survive. You know, we're doing a little better at that now because we understand it and have ways of trying to keep patients alive while we get their temperature up. But this turns out to be a direct function of platelets. If you put platelets inside a couette viscometer, just one cylinder inside the other and spin them to shear them, they simply stop activating at 30 degrees. And so that whole initial mechanism for causing platelet plug formation in primary hemostasis is largely lost in cold patients.

And having a low pH, a high protein concentration, means that when you form the negatively charged phospholipid rafts on which the coagulation system localizes. If you have more positive charges around, you neutralize those and reduce the binding of the clotting factors and the co-factors to that negatively charged phospholipid raft. And here you can see an activity curve for the Xa Va prothrombinase complex on cellular surfaces. And if you have normal coagulation at 7.4, at 7.2 it's only half normal. At 7 it's only a third normal. And at 6.8 it's only a fifth of normal.

Clot contraction, basically once you set up a fibrin network, you know those platelets with their pseudopods reach out and grab ends of it and kind of pull the net together. And the combined effect of all of this is to tighten the clot, to pull the edges the wound together, and to pull the clot accumulation out of the center of blood flow and lower it toward the surface so that blood flows around the place that was injured. And you can actually get more blood flow to bring more factors to help you make that go further.

And it's possible to build devices. This is one that was described last month in Blood, that actually looks at clot contraction. And you can see it in this cue that the clot which originally starts here contracts with time and the area that it occupies can be plotted. And one can look at the speed and the dynamics of clot contraction and then do experiments in such a device to study clot contraction, something that has historically been very difficult to do.

The upper picture shows a clot in a red cell free system. You can see the fibrinogin is mostly straight. The platelets kind of form nodes and pull the clot tight. When there are a lot of red cells in there they kind of get in the way and you have to kind of scrunch them down to make the clot work.

Massive injury leads to rapid consumption of clotting factors. You know, we're used to thinking of clotting in terms of single injuries. You know, the classic way it was studied was with a 1 by 9 millimeter laceration made by a device called a bleeding time template. A number 15--

Scalpel. We don't do them much anymore, but they actually are a very nice standard injury model.

You know, but if you get hit by a bus you end up with billions of endothelial microtears. At the bottom of each of those-- normally you've got this nice layer of endothelial cells covering your blood vessels. And all of them are exposing thrombomodulin. So if you make some thrombin by accident, it binds to thrombomodulin, it gets twisted, so now it only activates, rather than other clotting factors, it activates protein C and protein S, which in turn turn off factors V and VIII.

But now you get hit by that bus and you have millions of endothelial microtears. An at the bottom of each of those places where endothelial cells have been separated, you're exposing tissue factor. You're exposing type 3 college and Von Willebrand's factor. And you're binding platelets and you're activating the clotting system. At the same time that you're making thrombin, that thrombin is binding to the thrombomodulin in normal cells.

You know. And so you're activating protein C, which in turn inactivates the V and the VIII which are the co-factors for the last two--

steps in the clotting system. And it inactivates plasminogen activator inhibitor so that your plasma and your fibrinolinic system is simply running wild because you're secreting tissue TPA, and you're not inactivating it.

Now, high concentrations of fibrinogen and thrombin lead to the very rapid removal of the activation peptides on fibrinogin to make fibrin monomer. And those monomers will stick together to form fibrin gel, and then they'll get cross-linked with factor XIII to form fibrin polymer. And if you have high concentrations of thrombin you do this fairly quickly. And the ratio of nucleation to chain extension events and laying down of more on the top of existing chains works very well and you get these very nice, big, heavy, strands.

And again, in the presence of high concentrations of thrombin you activate this protein called the thrombin activated fibrinolysis inhibitor, which goes along and chews the lysine ends off. So there's no place for plasmin to sit.

If you activate this slowly, you know your ratio of chain extension to nucleation changes. And at the same time, you don't make taffy. So you have these wider open mesh works into which plasmin can intercolate and sites for it to bind. You know, drugs like tranexamic acid or lysine analogs that kind of confuse with the plasmin.

But in their absence, you know, this kind of clot is quite stable. That kind of clot is very rapidly chewed up. You've got high concentrations of the enzyme. You've got large amounts of surface area. You've got binding sites present.

And all of these factors work together. This is a study out of Denver. Ned Cosgriff and the group put it together then.

Basically, if you have no risk factors for becoming coagulopathic, you know, the chances that patients would have trouble with severe bleeding was very low. But be profoundly injured, have an injury severity score of 25, and you have about a 10% chance of being coagulopathic. Be hypotensive and being actively resuscitated and diluted, and it went up. Be acidotic, be cold, and it went up. Be all of those things and your chances of not being coagulopathic were essentially nil.

OK. Even so, we used to think that the coagulopathy came on slowly and was largely related to things like dilution. And then in 2003, in June issue of the Journal of Trauma Karim Brohi and his colleagues at the Royal London described 2,000 people who were brought to the Royal London by helicopter from accidents along the ring road who had received less than 400 ml of crystalloid fluid on their way in.

And what they pointed out was that about a quarter of them had an elevated PT that was at least 1 and 1/2 times normal. And that the more seriously they were injured, the more common that was. And if they had it, they had four times greater chance of dying. And this was called the acute coagulopathy of trauma.

A month later, Jana MacLeod and her colleagues at the Ryder Trauma Center in Miami published a retrospective review of 20,000 direct admissions and the relationship of their PT, whether it was normal or abnormal, and they used just 1.3 times normal as the definition of abnormal.

And looked at mortality. What they showed was is that the PT was commonly abnormal and predicted a 35% excess mortality.

The PTT was uncommonly abnormal but predicted a 400 fold excess mortality. So the PT is sensitive, the PTT is specific.

Now, we tend to use a number 1.5 to describe as the transfusion trigger for plasma. The study came from this hospital. Rich Counts and John Carrico are authors on this paper. And unfortunately, you know, what they did, they looked at a bunch of profoundly injured trauma patients and asked, at what point do they bleed spontaneously wherever we handle their tissue?

And on average, in the about 90 patients they did, that number turned out to be 1.5. But you'll notice that there were patients well above that who didn't bleed, and patients well below that who did. What's going on?

Actually, that same month that Jana MacLeod published, I published a kind of theoretical discussion of why I thought all this should happen. And it's just based on my knowledge of blood products. I said look, you add a unit of red cells, a unit of plasma, and a unit platelets together, and what you're giving these patients is fairly dilute.

But I went back a couple of years later and at Baltimore Shock-Trauma took all the admissions from 2000 to 2006. There were 35,000 of them, of whom 5,600 had an injury severity score greater than 15. So these are seriously or profoundly injured patients. And in the narrow range between an INR of 1 and 2.2, we could demonstrate kind of a stepwise increase in in-hospital mortality based on their admission INR.

And unlike that kind of magic number of 1.5, here it's a continuous function. Penetrating injury, big holes are a little worse than lots of little holes and with blunt injury, but it's essentially straight. And even for people with absolutely normal INRs, you know, between 0.8 and 1.2. To be in the upper half is to have twice the in-hospital mortality of to be in the lower half of normal.

And, you know if it's continuous function, if that patient is your loved one, where is the transfusion trigger?

Now, you talk to hematologists, and they'll say an INR should only be used to calibrate warfarin.

35,000 people. What do you need?

I say, Jana MacLeod did another 20,000, Karim another 1,000, you've got 56,000 people.

OK. If you then go back and say, OK, which of these functions matter? You know, the INR? The PTT? The fibrinogin concentration? The platelets? The more severely injured you are at any of these cut offs, the greater the prevalence of the abnormality.

The more disruption you've got, the more endothelial microtears you've got, the more of that clotting and break down process DIC you've got going on.

If we set those numbers at the classic transfusion triggers of an INR of 1.5, or a PTT, or fibrinogin of 100 milligrams, or a platelet count of 100,000, the problem appears to go away.

But if you go back and look at them individually, you know, if the ISS is in the moderately injured position there's little effect. But the more severely injured you are, the steeper that slope becomes. This is a function of the capacity of the clotting system versus the extent of injury. And you very rapidly in profound injury exceed the capacity of your clotting system.

Remember, it's only two teaspoons of fibrinogen and two teaspoons of platelets.

And for the PTT you get almost exactly the same functions, except that if you're about 1.5, 55% and 90% mortality. The PT is sensitive the PTT is specific.

Fibrinogen does the same thing. And it does it all the way up. And the platelet count turns out to be the worst offender of all. You show up in the emergency room with 50,000 platelets and severe injury, and you have a 93% mortality.

OK. So what do we do here? A couple of years ago Wayne Chandler put together for us this emergency hemorrhage panel. Basically we get you a hematocrit, a platelet count, a PT, and a fibrinogen measurement, and get it back to you and 14 minutes.

We don't use the PTT because it can be confused by lupus anticoagulants. But you really don't need it. You know, there is a one to one correspondence between the hematocrit and giving red cells, between the platelet count and giving platelets, between the PT and giving plasma, between the fibrinogen and getting cryo precipitate.

You know, inactive bleeding. If you simply give plasma, and platelets, and red cells, in 1, to 1, to 1 unit ratios you can usually stay ahead of this.

And here is one of those papers that Wayne Chandler wrote. He put the TEGs in the UW operating room in 1985. He put together our emergency hemorrhage panel. Talking to him last Thursday downstairs, he's still here. Still working. He's the head of the lab at Children's now.

OK. So here is a 19-year-old girl that Joe Cuschieri took care of two years ago. She was in a motor vehicle accident. She was t-boned. She ended up with a grade five liver laceration, right renal evulsion, an inferior venacaval tear, right acetabular fracture, and femur fracture.

And again, as you can see, she came in and dropped her pH down to 7. Her hematocrit, when she came in, was barely 20. Her platelet count went down to 18 at one point in the second hour she was there. Her prothrombin time came in at 33. And her fibrinogin came in at under 100.

120 blood components later, you know, they had it under control. They very rapidly corrected it. We have lots of measurements and you can watch what's going on.

Emergency hemorrhage panel you can redo every 20 minutes in a situation like this. And you can actually follow it in the lab we do in the blood bank, we you know, we'd call them up and say, I think you want a little bit more of this or a little bit more of that. And we do that for you. A month later she walked out of the hospital.

OK. So there actually is this device called a TEG. And a thromboelastogram is basically a cup full of blood with a pin hanging in it. And if you ever so slightly rotate the cup, nothing happens until the blood begins to clot. At which point it ties the cup to the pin and you start rotating the pin with the cup. And if you do that against some resistance with a torsion wire, as shown there, you hang a mirror on the torsion wire and shine a light on the mirror over to a piece of moving photographic paper, it will paint this pattern. And that's the way the original ones were built in 1947.

You know, nowadays they're built with strain gages and they're all electronic But, you know, the numbers and the stuff that comes out of that is based on those original measurements. And so when you start, the paper is moving up slowly.

Initially there's a time when the blood is liquid. But finally you get enough fibrinogin to-- fibrin to bridge from the cup to the pin, and you start transducing force. As you do that you reach some maximum amplitude, which is in sense, a measure of the strength of the clot. OK?

And here's the same picture rotated on its side. And so there's an R line, which is the length of time from the initiation of the clot. And you basically do this either by putting the blood in the cup and letting the kaolin that's they're activate it or you do it just by recalcifying citrated plasma whole blood. And you get a measure that's how long it takes from the time you activate it until you've actually bridged across the pint to cup distance.

And then it takes off and you can measure either the slope at which it takes off, the angle, or a distance until it's a certain degree of force transduced, called K. And finally, an MA. And then, at the end, if the clot goes away you can measure how much of the strength is lost over a certain period of time.

And you can look at patterns. If this is a normal, patients with hemophilia take much longer to initiate, and their clots grow much more slowly. And more importantly for the hemophiliac, they tend to break down a day later. Patients with thrombocytopenia don't pull that fibrin net together as well and end up with less strain. Patients with fibrinolysis make that clot. And patients with hypercoagulability make it sooner, and perhaps stronger.

The problem with this is that these measurements aren't linear and aren't terribly reproducible. Here is an experiment in which we are simply looking at the effect of platelet count on the strength. At fixed fibrinogen concentrations of about 270. And, you know, the more platelets you have the tighter you pull that net together. And so these numbers-- you can get the same number at varying ratios of fibrinogen and platelet counts.

And in, fact the opposite happens as well.

But even stranger things happen. As you become anemic, the fraction of your blood that's plasma increases. And if you're measuring at constant fibrinogen concentration-- we measure fibrinogen in plasma. The more anemic you are, the more plasma you have. And so actually, the more anemic you are, the stronger your clot as measured.

The red cells soak up nitric oxide because hemoglobin binds it. And, you know, that in a sense activates platelets. And so you get a whole set of rather strange interactions.

But here is the maximum amplitude in the presence of poisoning the platelets an the absence of poisoning the platelets. You know, done at varying fibrinogen concentrations. And you get this nice set of curves. On the other hand, you make exactly the same kinds of curves by doing the fibrinogen an varying platelet concentrations. And so you really don't know where you are given any particular number.

You know, they hold conferences, and we've held them now every couple of years for almost 30 years, to evaluate and try and decide what the place of TEG is in evaluating coagulation factors. You know, the hematologists never use the test. The ones at the UW are used almost entirely by the cardiac surgeons.

They use them to tell themselves when to transfuse, but you know, if they just look at the patient and say the patient's bleeding, transfuse. You know? And then you apply some simple heuristics to it. You know, if you've given two units of platelets it's time to switch to plasma. You know, they would do just as well.

You know, last year before the AAST meeting, Sandro Rizoli held a working group and put together and then published in the Journal of Trauma a consensus panel. I sat on that panel. And we basically agreed that TEG can provide you some information that fibrinogen is low early, but you could also measure the fibrinogen.

And the English did a similar one to decide whether or not they were going to put TEG out in their hospitals around England. And we really couldn't find many particularly useful reasons to do this.

But the Europeans are persistent. And this is a study that just came out in November. You know, from four big centers in Europe. Oxford, London, Copenhagen, and Oslo. And what they did was they enrolled 808 patients, all profoundly injured trauma patients. And measured their PT and PTT and then did their TEG measurements.

And what you discover by looking at this is that compared to the standard INR and the standard tests, none of the TEG tests performed as well as the biochemical tests in terms of the areas under the receiver operating characteristic curves. And in their discussion they point out that it's really never been shown that these tests perform better than the ones that we have the we can do repeatedly, and cheaply, and in a highly reproducible way.

And you know this is interesting, because most of the authors on that paper are my friends. That's something I've been telling them for, you know, much of a decade.

So where do we stand? There are really no coagulation tests that are perfect for understanding the acute coagulopathy of trauma. The most important thing you do is look at and try and guess how sick the patient really is.

Conventional platelet counts, the PT/INR, and the fibrinogen provide some mechanistic insight into exactly what's going on. They do tell you when to transfuse, and they can be followed rapidly and cheaply.

Again, here's a 36-year-old man left in front of a firehouse in West Seattle, pulseless and with a gunshot wound in his groin. The firemen came out and put direct pressure on his groin. And, you know, did CPR on him and got him here to Harborview where we got a clamp on his aorta.

You can see he came in with a pH of 7.1, a hematocrit of 20, a platelet count that rapidly fell, and a prothrombin time that was wildly elevated, and a fibrinogen that was low, and we were able to successfully resuscitate him and get those numbers to go right back into the normal ranges very quickly. Using the acute hemorrhage panel that way is a great way to have somebody standing, watching a resuscitation and telling you whether it's really working.

The promise of TEG is that it's faster, but what Wayne Chandler did was, is he took the element that was slow, the Clauss fibrinogen, which is normally run for 30 minutes, and just-- but all you do is you add thrombin to plasma and watch the fibrin clot. He just read it at 10 minutes rather than the classic 30 and he gets to you at 14. They say you see the whole clotting process but in fact you don't. Clotting starts with platelets and there's no endothelium in the cup and pin model. You know, it's all plasma. It's all driven by kaolin. You could do exactly the same thing with a kaolin PTT.

You can see platelet function, and this is true, but it's buried in a maze of other things. And you can see fibrinolysis, and that's true. But what's going on-- fibrinolysis in acute injury is also fibrinogenolysis. And so measuring the fibrinogen gives you a perfectly good measure of what's happening to your fibrin and your fibrinogen. And you need one to make the other.

Here is one of John Holcomb's patients down in Houston. This is a young man who had an unfortunate interaction between a motorcycle and a guard rail and tore off a leg, flailed a chest, broke a pelvis, tore off a leg and an arm. You know, and you see an emergency room TEG there that shows a very rapid onset of coagulation and a very rapid onset of fibrinolysis, and he ends up with nothing and he bleeds like mad.

This is the reason why you want patients like this on tranexamic acid. You know, but if you look at the pictures of this man and his-- the stump of his leg is just flailed tissue. You can say, look this guy's got more than a pound of damaged tissue. He's going to be in profound injury and this kind of DIC. You don't need a machine to tell you that.

Organizations like the College of American Pathologists, the English National External Quality Assurance Scheme, hematology groups every couple of years get together and look at the latest versions of the TEG machines and decide they really cannot quality control them. If I take my plasma and repeat the measure on my normal plasma--

Five times, I get five slightly different answers. If I do it five days in a row, I get different answers. If I hand it to somebody else, they get different answers. It's not a very stable test.

You know, it's dramatic. It looks good. But we have not been able to turn it into a highly useful, highly accurate test. Whereas the PT, and the PTT, and the platelet count, and the hematocrit just get better year by year.

So what's the excitement about? If you go into PubMed and put in TEG and some of your favorite authors, you know, Gene Moore has 25 papers on TEG in the last couple of years. But, Gene Moore has, what, 700 papers published? And he's got them on strange things like blood substitutes and drives us all crazy with, you know, kills people.

John Holcombe is my very good friend and, you know, we've written 35 papers together, but he's got an engine down there in Houston that cranks out papers, and he's got 16 of them. Marty Shriver you know, has 7 TEG machines in his lab down in Portland, and he has got 14. Wayne who's been doing this for 30 years and sits on all the boards has 4. Eileen, me. Yeah, actually I've got 2 somewhere, but they don't show up in PubMed.

So at Harborview we have the emergency hemorrhage panel. 50%, 14 minute turnaround, 18% 18 minute turnaround time. Dr. Bolger has the TEG in her lab that we were given to do part in a proper study. We're really not interested in setting them up and running them. We just don't think they're worth it. And we think they would take the limited time we have away from doing the test that we think is going to actually provide you more utility.

At the University we have the emergency hemorrhage panel and everybody but the cardiac surgeons use it. We've had TEG for 30 years.

Here at Harborview we are using 60% less blood than we did 12 years ago. Across the board. It's red cells, it's plasma, it's platelets, it's cryoprecipitate. You know, that's because we've learned how to resuscitate people and we've learned that low transfusion triggers are tolerated.

And that grade five liver injury which used to be 76% fatal, last year the Houston group published a series with a 6% fatality rate. 68% of those people were not operated on. Grade 5 liver injury is almost a pure play in hemorrhage control. We can do it and do it very well just with balanced resuscitation. And, you know, interventional radiology.

And you know, blocking.

And so, I would thank you.

[APPLAUSE]

Yes?

SPEAKER 1: It would look like one of the problems with TEGs is that the measures we get out them are really incredibly naive and stupid. Like, K, R and alpha. Like, those are just looking at a graph and throwing a protractor on it. Is there anybody doing more fancy, functional analysis to get a better image of clotting from all that data?

JOHN HESS: Well, I mean, what do you want? You know, the R is the length of time it takes to go from initiation, adding the calcium, to the first time you actually bridge the clot.

SPEAKER 1: And you've convinced us pretty well that that is a number of no interest.

JOHN HESS: Well actually, it's exactly the way we measure a PT and a PTT. We re-calcify, either in the presence of tissue factor or in the presence of kaolin, and measure the length of time until the clot begins to form. You know, what we're doing.

But we've spent many years perfecting the PTT measurement and the cuvettes, and the ways we measure it. Here's a fairly clumsy way of doing it that takes eight minutes, you know, and we've got the PTT down to 12 seconds. Of course we can get it to you faster. You know, but it is the same measurement. Once you start building a clot across it, you know, where it ultimately gets to is a measure of the-- some combination of the amount of fibrinogen you've got and how tightly the platelets pull it together.

There's not a whole lot more information in that. There's a slope. There-- and you can take the first derivative of it and have a-- which is functionally a measure of thrombin activity.

SPEAKER 1: The K and the alpha are totally redundant, but--

JOHN HESS: Yeah.

SPEAKER 1: --the max amplitude to the one most people look at the most.

JOHN HESS: Yeah.

SPEAKER 1: And that one is completely dependant on all the factors, so.

JOHN HESS: Yeah.

SPEAKER 1: You know, I mean, you'd think that you could look at the shape of it, which is what everyone says in the cardiac rooms when they're talking about these things, and get more out of it that way. Is there some more formal way of approaching that than eyeballing it and saying, yeah, it's OK. Because that's pretty much what we do.

JOHN HESS: You know, you give people like Pari Johanssen who've been doing this for a decade, you know, and 808 patients and let the measure areas under curves, and measure all the individual factors, and turn their mathematicians loose on it. And the answer is, is heaven. It's a curve. And, you know, apart from slope and, you know, I mean you can do differential equations on it. You can measure a slope and measure its rate of change.

SPEAKER 1: Well, I mean, what we do functionally is we get the numbers back long before we get the TEG back, and everything has been corrected by the time we can even interpret that.

JOHN HESS: Sure. Which is why in our lab we've decided that this is one of the few tests where we drop everything we're doing and get out for it. And try and get it out quickly. And believe that there really is this one to one correspondence between what you see on the panel and what you should give. It's a kind of slightly better version of the old, if you're breathing yellow, give red, if you're breathing red, give yellow.

SPEAKER 2: So what was the failure of the system with the infant in the first place?

JOHN HESS: Well, just that-- remember came in with 300,000 platelets. And platelets, you know, you come in to a trauma center with your normal platelet count. It falls in the first hour or two after you get there. And they kind of missed that.

We fixed the clotting system because that's what appeared initially to be wrong. We got the kid's crit. But as his platelet count fell over the next two hours and he started to re-bleed, they didn't treat what had changed. And got kind of caught up in the idea that you don't treat transfused platelets over 100,000.

Somebody will yell at you. We-- at the blood bank we don't yell at you. Were available. Call us.

SPEAKER 3: [INAUDIBLE] is the balance transfusion in a non-trauma? So when you have like a focal-- what I'm thinking is like a GI bleed. So if you had someone with an ulcer or a diverticulum that happens to really open up and they need massive transfusions but it's a small--

JOHN HESS: You know, the only study that looks at that is the Brazilian one that was in the New England Journal three years ago. You know, which said that transfusing patients with GI bleeds actually increased their mortality.

SPEAKER 3: But those were not hemodynamically--

JOHN HESS: Those were hemodynamically relatively normal patients. We really have worked this out in trauma patients over the last 10 years. I mean, this really started in the summer of 2004, John Holcomb called me from Baghdad and said, I just had a kid who came in damaged by an IED. He got 18 units of red cells and died before we ever got the plasma thawed. You know, I told him to thaw AB plasma and have it ready for the next kid who came in.

And the rest is kind of where it's gone since then. In 2005 we held a workshop, in 2007 we published the guidance in the Journal of Trauma to use one to one. Last--

SPEAKER 3: Do you think it applies, like in a MICU. If you have an RP, like a met transfusing 10, 15s.

JOHN HESS: Yeah. We published this year in the New England Journal the recess trial. A study of whether old blood is bad, and did it in patients with repeat mid-line sternotomies for major vascular surgery. As we're going back through the data what we can see is, that if you've got six units of red cells and two units of platelets and didn't get plasma, you know, in the about 350 people that fit in that group, the ones that didn't get plasma had 17 deaths and the ones that did had two.

SPEAKER 3: And these are all comers?

JOHN HESS: These are all comers within a randomized clinical trial. You know, so it appears that if you've gotten six units of red cells you'd better be balancing that.

SPEAKER 3: For any reason.

JOHN HESS: The resuscitation. But that's the only piece of evidence that I've got, other than the sort of general sense that you're going to screw up the coagulation system if you let it get dilute.

SPEAKER 3: So just treat any massive transfusions any [INAUDIBLE].

JOHN HESS: Anybody. And use the standard definitions. The critical administration threshold. If you administer three units of red cells within 60 minutes, you're probably dealing with a massive bleed. If you do it two hours in a row, that's cat 1, 2 in a row is cat 2, it's only worse. You know, that's what Sullivan is publishing out of Memphis.

OK. Thank you.