Our next speaker is **Dr. Margarethe Heiden.** Dr. Heiden joins us from the Paul-Ehrlich Institute in Germany. She specializes in hemostaseology, blood components and stem cells. She's the head of the section of transfusion medicine. Her main responsibilities include marketing, authorization of blood components, including red cells, leukocytes, platelets and she also is a member of the Task Force for Blood Safety at the Institute and a member of the National Advisory Committee. Welcome.

DR. HEIDEN: Thank you. Thank you very much for the kind introduction. Thank you for the invitation. And first of all I have to say that I cannot say anything about the European experience, and that's why I am speaking about the German experience, and the second thing is I got the impression from this day and especially yesterday, that much information was already said but and hopefully I at least will add something new ideas, I hope. Okay. European legislation regulating blood components, we three main directives, which involve the regulation of blood components, blood collection, the first one, and its technical directives giving standards of quality and safety for collection, testing, processing, storage, distribution of blood components, and the point is that details going over these standards have to be regulated by any country depending on its technical feasibility, also its epidemiological situation and also economic situation. The other two directives, giving standards for screening tests, IVD directive and the medical device directive, giving standards for apheresis and blood bag systems, and son on, these directives regulate the marketing, the coming into the European market for these medical devices in IVD but the use of these depends again on each country in Europe. Okay. Our national legislation for blood components Germany, first of all, is to say that blood components are considered strict according to our definition in our drug law and the blood establishments need a manufacturing license given by the regional authorities together with the Paul Ehrlich Institute, the competent authority for marketing authorization of the blood components and the German Transfusion Act regulates collecting, details in collection testing, also donor protection details and use of blood components. We have different parties cooperating in

Germany for blood safety. I think it's similar like here in the United States and in other countries. We have the competent authority for marketing authorization of blood components for hemovigilance and IVD vigilance. We have the national authorities which are doing GMP inspections and also surveillance. We have German Medical Association, which puts national guidelines together with our institute. We have the Robert Koch Institute that's responsible for donor epidemiology. And we have also the National Advisory Committee Blood, perhaps similar to this Advisory Committee, and in this Committee all the parties, the cooperating parties are involved. That means doctors of different types, hematologists, pediatrics, and so on. Patient organizations, the Robert Koch Institute, the Paul Ehrlich Institute, scientific societies, representatives and also representatives from patient organizations. It is to note that the representatives from the Robert Koch Institute or from our institute are not allowed to vote when recommendations are prepared. Okay. How are these cooperating parties involved in decision-making for the blood safety? We know they have three main strategies for decision-making. It's something a little bit mixed up but mainly for historic reasons it's development, decision-making in Germany.

Okay. We have one, the first strategy, we have blood components are suspected to cause concern. The source of concern may be scientific literature, discussion in different societies, and of course striking hemovigilance reports. Our drug law gives us a definition, what is concern? There is a provision. Which is very important, I think. "Drugs cause concern, if according to the state of scientific knowledge there is reason for the suspicion that their use according to their determination leads to harmful effects, which exceed a degree which would be tolerable according to the current state of knowledge of the medical sciences." And, I think that this implies immediate and annual and continuous reevaluation of the drugs, of the safety of any given drug. Okay. Then evaluation of all the data, the Paul-Ehrlich Institute has to substantiate the concern and to start a graduated pharmacovigilance plan. If the concern is already substantiated, then we start from step two of this pharmacovigilance plan. That means we announce a measure. And, it starts with a written hearing and depending on the impact on availability of blood,

on the economic pressure and so on, a public hearing will follow to discuss all the details of the impact of the measure. And, then the step three, official order by the competent authority, in case of blood components and blood derivatives and so on; it's the Paul Ehrlich Institute. And example of these orders is introduction of screening, NAT screening for HCV, HIV-1, for anti-HBc antibodies, donor deferrals or travel deferrals because of variant CJD, travel deferrals for SARS, West Nile virus and chikungunya. If there yet some doubts we start with a step one of the pharmacovigilance plan. That means we start with an exchange of information with the blood banks and even during step one and also during step two, the main questions which have to be addressed to the blood banks, questions, for example, is it technically possible, will the measure have an influence on the availability of blood components, what impact will it have on the cost of the blood components, and if it's also in our interest to know if we have one or more supplies of a certain technique or a certain test. Okay. Then after all, even after the official order, any blood bank has the ability to make an appeal. The second main strategy for decision-making is used when we don't have substantiated any concern or if you have a new kind of testing or manufacturing which promises a higher safety or higher overall blood component quality but the hard, severe scientific evidence is missing. In this case the matter will be discussed with all parties, by the national advisory board, and depending on the outcome of the discussion a recommendation may be given. This recommendation has not set a certain concise deadline like an order by the Paul Ehrlich Institute but it will say that in the near future the blood establishment may follow the recommendation. Example for this is, have been leukocyte depletion, sterile docking procedure and especially a good example is this introduction of predonation sampling and we just at the end of last year we collected the data from two years after introduction of the predonation sampling of the bacteria, quality control testing, and we saw that indeed we got a significant decrease of contamination in red blood cell concentrates. There was no significant difference in the contamination rates for platelet concentrates

and there's also no significant different between pooled platelet concentrates and apheresis platelet concentrates. The results will be published soon.

The third strategy for decision-making is a new kind of testing or manufacturing is available; however, according to the current assessment of safety and quality of blood components in our country there's no need to give order to a general use. That means you can only give order to a general use of a new method when you have a concern. It's according to our Act. But, in this case we have a large advantage, then we can, then nevertheless single blood establishments can apply for this new or for a changed marketing authorization in order to introduce the new innovative technique into their product program. And, I think it's a great advantage for us in Germany, because we have the possibility to stepwise introduce these new techniques and we have at the same time we have different methods on the market, and we can even compare the postmarketing surveillance data from the different, not quality but the difference techniques during our hemovigilance. An example for this is screening for HBV by NAT, it's not so exciting, but SD-inactivation of pooled plasma, MB light treatment of single donor plasma, and Amotosalen light treatment of platelet concentrates.

Okay. The next slide, why we use the strategy number three for pathogen inactivation? In Germany we have around, about 6 million blood components instituted per year, more than 4 million red blood cell concentrates and about 400,000 platelet concentrates per year, 50 percent, 50 percent from pooled and from apheresis platelets. And the residual risk rate of undetected donor infections calculated, adjusted incidence, window period model -- that means it's based on the donor incidence of the given infection or infectious disease or infected particle and depends also on the window period. And this again depends on the sensitivity of the assay. And you'll see it's based on data from donor epidemiology from 2000 to 2002. And, unfortunately this method cannot calculate the testing for hepatitis -- antibodies -- but therefore the value for HBV, 1 to 620,000, I think is much better now in Germany. Okay. Next situation from our hemovigilance, for the three main viruses, transfusion-transmitted, viral infections assessed as probable. On this one, shown on the slide, we see that until '98, had a lot of

HCV transmissions despite anti-HCV testing and especially the 11 in 1998, there was a case of a combined test period with a noncompliance of performance of Lobeck (phonetic) procedure and though we had only in this year, nine contaminated patients, from one donor, here, the three cases until 1980 from HIV transmissions, had been two of them window period transmissions and one of them single test failure from antibody testing. With introducing HCV, NAT, we had only one case in 2004. After introduction of HIV NAT, we had one case, unfortunately, last year. The decision-making for the detection limit for the HCV and HIV, one NAT was made based on scientific literature, on experimental data, and on the evaluation of the cases from the hemovigilance and as was seen yesterday HIV as well as HCV have a high multiplication rate after infection and you have a steep increase of virus titer. And, so, a decision was made based firstly on this knowledge of the steep increase of the virus titer and then also of the feasibility for the introduction of the method into blood bank routine and it's been done by medical testing though we have a limit for HIV of 5,000, no, 10,000 international units per MIL and for HCV 5,000 international units per mil plasma of one donor. And, we introduced in 2006 anti-HBc testing and there we see antibody testing after a long, long story of discussion and this long story of discussion depended on initially a very bad specificity of the anti-HBc antibody tests and also on the hope that the HBV NAT will overcome the problem but it didn't and so we introduced anti-HBc antibody testing. And I think it was very useful because cases slowed down rapidly and in this period nine frequent donors had been discovered which had been proven to be infectious by single HBV NAT.

Okay. This is the valuation. Pathogen inactivation of blood components is not required as a nationwide measure with respect to risk of HIV, HCV, and HBV transmission. It may be required in altered epidemiological situations as shown yesterday but up to now in Germany we don't have really problems with all the other bacteria or viruses, and we have only one transmission of malaria since 1994. And again, however, establishments can apply for a marketing authorization of pathogen inactivated blood components. And, they did it already and they have already their marketing authorization.

Another problem is bacterial contamination. These are data from our hemovigilance report. We have, in sum, 61 cases in this decade assessed as probable. These are only severe cases, severe septic cases, and in this decade we have nine deaths and in the last years six by platelet concentrates so we can say, according to one of the first slides, we have one patient died on average per year or per 400,000 platelet concentrates administered. And we think that action here is required but what kind of action is required? We've seen that pathogen inactivation at least as seen from the experimental data may not be as safe as expected and screening for bacteria may not detect critical components. The question is, do we have further solutions? That is a picture of experiments made by Thomas Hunter (phonetic) from our institute and it clearly showed that the Amotosalen light treatment of platelet concentrates do not inactivate spores, and it's known from experiments that also some Pseudomonas strains not so efficiently inactivated. And I think here the French hemovigilance data may give an answer, if pathogen inactivation has really survived the right way to avoid severe septic infusion reactions.

The screening for bacterial contamination the right way, it is presented, the sum of six recent studies on screening of bacterial contamination by a culture method, BacT/ALERT, used since 1998 as a standardized quality control testing, and, but we have prepared with issuing as negative to date because it's hardly impossible for drug release and blood components are considered as such. Okay. A summary of these studies is that two million platelet concentrates have been tested and shortly there is one interesting, two interesting results. First of all, the platelet concentrates, which at a later time revealed to be positive and had been issued negative to date, nearly, the main part of the patients did not show symptoms but only three of them, there were 200 initially positive later on issued negative -- later on positive -- 276 didn't show symptoms and 3 of them did. And the most striking is that in spite of testing we have 6 fatal outcomes, 28 false-negative results. That means fatal cases are not avoided by screening. Okay. Further solutions to avoid transfusion-transmitted bacteremia, we've seen that platelet concentrates causing severe sepsis with fatal outcome had been

stored for more than four days. And by chance, if importance of the storage been shown in the study by Eder, one donor give a platelet concentrate by apheresis and two platelet concentrates were prepared from it. The one given on day three of storage with set direction to be handled and the second one given on day five of storage and the patient died. That means now we are thinking, is it wise to reduce storage time to four days? Together with, combined with the concise instructions to the transfusing personnel, how to handle septic reactions, efficiency, of course, had to be field tested and logistic problems had to be expected but perhaps also there will be an overall in quality because of shorter storage times.

Back to the strategy number three, how we are performing licensing of pathogen reduced blood components? We do it like we are doing licensing for any other component or any other biological, like for plasma derivatives and other drugs. In effect they have to show state-of-the-art pharmaceutical quality by experimental data of the applicant and sometimes which new methods produce also our own data. The safety has to be shown by experimental preclinical data and all these experiments and variation of experiments have to follow ICH guidelines, all guidelines for the validation of virus infection from the European Medicines Agency, and clinical data have to follow good clinical practice. And, efficacy, the clinical data should prove noninferiority but to tell you the truth, one cannot expect that you don't have any data of diminishing, or diminishing of the efficacy of a treated component. It's been often true for the plasma derivatives but it has to stay in a range which doesn't do harm to the patients.

Okay. And then if you see some problems with the -- not problems but some things with the product with your license, then it's a normal procedure to license under conditions, for instance, to introduce specific impetus controls or quality controls for release to introduce into package inserts with specific safety information and, of course, postmarketing surveillance really done with a yearly safety update and, of course, immediate suspicious case reporting. One of the examples of the older product is the SD-treated pooled plasma. We clearly have a lot of advantages of this product. It's relatively homogeneous because of the pooling. It's particle-free because of sterile

filtration of the final product and therefore hardly allergic, we do not see allergic side effects and clinicians take it very voluntary and we like to take it we didn't show any case of TRALI or any antibody dilution by pooling and we have an official batch release. That means we know all of the quantity of this product. In the disadvantages up here, we have no pathogen inactivation capacity against non-enveloped viruses, that means not, Parvovirus B19, HIV are not inactivated but there are measures in case to overcome this disadvantage, like they have a procedure, immanent inactivation of important plasma proteins like Alpha-2-Antiplasmin and Protein S, and we may have variant CJD spreading by pooling. Okay. Then we get the order to introduce special text in the package insert, with regard to Alpha-2-Antiplasmin deficiency in the product, and we gave hints to the side effect of the risk of B19 and HIV transmission, and as it in European line, European distributed product. It has to follow the European pharmacologic properties and therefore because of the disadvantages into the pharmaco-properties it has to be introduced in the necessity of Parvovirus by B19 testing with a limit of ten to the three, international units per mil for the plasma pool and it has to be introduced, a batch release test for anti-HAV antibodies with a limit more than one international unit and the batch release test for Protein S and all the proteins here is yet in this discussion; that means it will come but limit is yet in discussion. Another example is Methylene Blue/light treated, fresh frozen plasma, single donor plasma. Again in the package insert we have some things, again precautions for use, a hint to perhaps impaired styptic capacity of the component, hint to maybe allergic reactions against Methylene Blue and its photoderivatives and the possible transmission of HIV and Parvovirus B19.
There are indications on the pharmacologic properties of, especially of the diminished fibrin polymerization capacity of Methylene Blue/light treated plasma and however that it is say this diminishing of the fibrin polymerization capacity to a large, large extent depends on how the plasma is handled, how the manufacturing is done.
And, these are more of the data from other countries, from Spain, especially, which claim this worse quality but we didn't see it at all in the product we

give the license for. And there are indications for preclinical safety data that Methylene Blue, photoderivatives have concentrations much lower than doses which gave toxicological effects in preclinical studies. And, one of the safety measures is to introduce an HBV test for, to have a really safe product. And regulates time and measuring of concentration was introduced for the quality control of Methylene Blue for the manufacturer. And, it's the same procedure was performed for Amotosalen light treated platelet concentrates and again in the package insert you have contraindications for known hypersensitivity against Amotosalen-HCI or psoralens. The main point is that newborns with hyperbilirubinemia which had to be treated with light of a wavelength less than 425 nanometers shouldn't be treated with, transfused with this, Amotosalen light treated platelets. As a side effect, again anaphylatoxic reactions are listed here in the text. And up to now, immunologic reactions by neoantigen formation are at the moment not known. As side effects also the possible transmission of nonenveloped viruses and the possible transmission of spore hormones is introduced in the text and the further point with side effect is that pyrogen load is not abolished by pathogen inactivation because the treatment doesn't remove pyrogen from the component. And, again, the pharmacological and toxicological properties of Amotosalen are listed in the package leaflet and again it's listed that there are no signs of phototoxicity, at least with the concentration which is in the component. Safety aspects, again, we have testing despite pathogen inactivation to reduce bioburden, and as a specific quality control it was introduced, the measurement as a quality control procedure for Amotosalen content. That means, to summarize, why we introduce pathogen reduced blood components despite an extremely low risk of transfusion-transmitted viral diseases, and it's clear that it adds to the already high safety achieved by pathogen testing. For instance, in cases of errors or test failures, we had sometimes already noticed, and it's important for people to prepare in case of new-emerging diseases without a test available and especially now and we are prepared in case of a pandemic without the chance of testing for new or for the pandemic pathogen. Yeah. And, I like this, that's why I have to show it again, different strategies we

have to supply the different wants. Thank you very much for your attention.

Dr. J. Vostal (FDA-CBER. Chief of Laboratory and Cellular Hematology in the division of hematology, the Office of Blood Research and Review)

輸血製剤に不活化技術を導入したことによって得られる利益（ベネフィット）と、それにより起こりうる損失（リスク）とのバランスを考慮しなくてはならない。ここで言うリスクとは、不活化による輸血製剤へのダメージ、不活化製剤の受血者への有害事象、製造者への毒性（これらの人々は高濃度に化学物質と接触する可能性がある。）、また環境への毒性（仮にこれらの薬剤が変異原性または発がん性を持つ可能性があった場合、その廃棄物が問題となる。）などである。不活化によりどのようなベネフィットがあるか、その対象は何か、そしてウイルス、細菌、寄生虫、そして特に新興あるいは未知の病原体に対する不活化の効果について述べてみよう。

まずベネフィットがなにかを考えるために先にDr.Doddによって提示されたデータのおさらいをしなくてはならない。これは現在の輸血製剤における細菌汚染のリスクを示しており、米国赤十字社とDr.Ederによって論文にされている、多くの製剤について試験を行った素晴らしいスタディである。細菌同定試験を行っていない製剤の汚染率は1/5000で、敗血症の発生率は1/75000である。試験で陰性だった製剤も同様に致死率は1/500000である。このデータを集めたところで米国赤十字は採血と試験の手法を見直し、試験をより最適化できると考えた。そのため、**初流血除去とバクテリア同定試験のサンプリングする検体血液量を増やすことにより、敗血症発生率を70-75%減少させることができる。これにより1/300000にすることが可能である。つまり今の輸血製剤の安全性レベルは検査と予防で保たれている。そしてこの検査という方法はきわめて良好なリスク対ベネフィット比を示している。製剤から抽出したサンプルで行われるこのテストは製剤にダメージを与えないし、製剤に何も加えないから患者への毒性も発生しない。更にこの方法は製剤供給の安定化に寄与にする。**つまり検査にお

けるリスク対ベネフィット比は非常に低く、そのバランスから検査のベネフィットは、それに伴ういかなるリスクよりも有意にまさっているのである。
そこでこのような解析を薬剤のまたは光化学不活化法に当てはめて考えてみるとベネフィットは現在のウイルス(1/150000)とバクテリア敗血症(1/75000)の減少ということになる。輸血による感染症のリスクが他の有害事象へシフトしないようにこのバランスシーソーはだいたい1/75000あたりとするべきである。そしてこれが無理な注文であることは次のスライドに示されるように**1/75000のリスクを排除することを確認するために必要なスタディのサイズである。つまり95%信頼度を得るためには200000人の受血者が必要となる。だからどのスポンサーも会社もこのサイズの研究を前向きに完遂することはあり得ない。**現実的には100人の患者のスタディを見ることは可能であろう。これまでのストラテジーはいくつかの有害事象における効果をみることや、何も副作用を起こさないことを示すスタディを行うものであり、それを証明することは可能だが、これだけの母集団のサイズは実際には市販後調査で可能となる。

ではわれわれは一体、不活化技術導入に対し何を危惧しているのか。
不活化製剤は種々の年齢や健康状態の異なる広い範囲の患者に静脈投与される、薬品と生物製剤の混合というこれまでにない混合物の作成である。**つまり危惧されていることは不活化に用いる薬剤が核酸と結合することであり、それは高頻度に変異原性と発がん性を示し、発がん性のリスクがあるかどうかを確認するために長期間の市販後調査を必要とする。更にもうひとつの危惧は細胞や輸血製剤そのものまでも傷害することが出来る光エネルギーの応用であり、さらにその薬剤はいったん活性化したらたんぱく質や脂質、細胞や臓器へ非特異的に結合する可能性である。**そしてこれらの化学物質によって引き起こされる傷害または傷害の可能性は体中に広がり、現在の同定ストラテジーでは検出が困難なのである。つまりこれまでの古典的なFDAを通過するための現在の製剤承認のためのストラテジーと同時にin vitroの実験によるphase Iを行い、これらのスタディで細胞生化学や細胞形態学に対する全体的な傷害を確認する。更にはそのPhase Iに加えて毒性の評価のために動物実験が行われることになるが、不活

化に使用される薬剤についてもこれらの試験が、行われ、in vitro study を通過し、そのスタディの結果、安全性が確認されたと聞いている。その相対的な安全性プロフィールを持っているので、製剤の体内でのカイネティックスを確認するためにラベルした薬剤を健常人ボランティアへ投与するといったスタディを含む、Phase II の臨床試験へと進めた。これらのスタディでは健常人ボランティアにおいて循環能力を失い、回復が遅れていることを示す結果がいくつか得られている。これにより実際更に機能面での効果に損失があるかどうかははっきりしなかった。

Phase II の次のステップはある特定の患者群に対して効果、輸血頻度、有害事象や毒性をみるための Phase III の臨床治験である。もし PhaseIII にクリアして承認が得られると市場に出ることになり、極めて稀なものも含めて有害事象のフォローアップを行うための Phase IV が必要になる。

ここで私はアフェレーシス血小板に対するシーラス C-59 について話をしたいと思う。何故ならこの製品が開発過程において最も進んでおり、彼らの Phase III の臨床治験の結果からは学ぶことがあるからである。シーラスによってなされたこのスタディは SPRINT と呼ばれており、その内容について情報を得ている。それは無作為化比較、二重盲試験の非劣性を証明するための Phase III スタディである。このスタディの目的は従来の血小板と不活化した血小板の止血効果における安全性を比較することである。スタディのエンドポイントは WHO の Grade 2 以上の出血を呈する患者の割合である。提示するのはこのレポートから直接引用した表である。この表にはエンドポイントである Grade 2 またはそれ以上の出血を伴った血小板の割合が示されている。これはかなり大きなスタディで不活化血小板 318 人、コントロール血小板 327 人である。いずれの Grade2 の出血イベントを見ても両群ともに出血をきたした患者の比率は同じである。この視点から言うと、このスタディは成功している。さらに彼らは出血部位別のデータも示している。ここで指摘したいことは血小板数や血小板機能に依存することが知られている粘膜下出血のイベントである。これには統計学的有意差はないが、**不活化処理をした血小板で皮下出血が多い傾向にある。**もうひとつ指摘したいことは

やはり統計学的有意差はないものの、呼吸器系の出血が若干多い傾向にあることである。これは少し遅れて症状が出るので留意すべき点である。同じ論文の中の表6ではスタディ期間内に使用した血小板と赤血球の量が示されている。血小板の総使用量はコントロール2041本に対して不活化群で2678本であり、4人の造血器悪性疾患患者に対する支持療法では30%も多く必要としていた。これをみれば、その数字がどこから来たかがわかるだろう。患者あたりの平均輸血使用量はコントロール群6.2本に対し、不活化血では8.4本と多いことがわかる。輸血の平均間隔をみてもコントロール群で2.4日に対して処理群では1.9日と短い。また同様にこれらの患者が使用した血小板の量も不活化処理した血小板の方が多く使用され、コントロール群で少ない。患者の使用した輸血量を見てわかるように、不活化処理は、患者の血小板の使用量を増加させており、実際にコントロール群に比べて患者に投与された血小板数が少ないということが問題の一部であろう。血小板製剤の基準値である製剤中の血小板数が 3.0×10^{11} 以下だった比率は不活化処理群で20%に対してコントロール群で12%であった。指摘すべきもうひとつの点はこのトライアルにおける赤血球の使用である。統計学的有意差はないものの**不活化処理血小板で支持療法が行われている群で、より多く赤血球が使用されている傾向にある。**両群において半単位ほどの差がある。そしてこの論文の表7では筆者らは血小板輸血後の反応についてまとめている。ここに示されているように両群において開始時の血小板数は同等である。**そして1時間後の数字を見てみるとコントロール群でおよそ5万に対して3.7万と有意に低いことがわかる。**血小板増加量を見てみるとコントロール群では3.4万に対して不活化群で2.1万であり有意に減少していることがわかる。同じことが24時間後（CCI_{24}）でも言える。**血小板数でも血小板増加量でももちろんCCIでも同じ結果、傾向である。**この結果に基づき、血小板数が処理によって少なくなった血小板製剤によって患者は治療を受けているということがわかった。論文中の表8では血小板輸血の不応性について述べているが、スタディの中で2つのエピソード（連続的に輸血を行ってもCCI1hが5000以下であった症例）が明らかにされている。さらにすべての血小板不応についての比較することが出来るが、コン

トロール群で7%だったのに対して処理群では21.4%であった。**不活化処理を行った製剤を投与された群で有意に多くの血小板不応が発生していることが明らかであった。**この観察で興味深いことは、免疫学的な不応については両群で差がないことである。つまり全体的な血小板不応は免疫学的な機序ではなく、多分、細胞のダメージに起因しているものだからであろう。そしてこのスライドではSPRINTスタディにおける止血効果の結果についてまとめている。トライアル自体はGrade 2以上の出血をきたした患者の比率のエンドポイントに合っている。しかし、**血小板効果、たとえば、血小板の使用量が30%多くなること、輸血間隔が短くなること、輸血後の血小板回復の反応が落ちること、血小板不応の発生率が高いこと、赤血球の使用量が増加することといった点では、このトライアルはうまくいっていない。**

以上の結果からある副作用の存在が浮かび上がる。たとえば、輸血の使用量が増加すれば輸血後感染症の遭遇する機会が増加するし、特に赤血球の使用量が増加すれば、赤血球にはこの技術は応用されていないのだから尚更である。血小板において30%使用量が増加し、赤血球の使用量も増加することになれば血液供給にマイナスの影響を与えるかもしれない。このトライアルはいくつかの論文に掲載されている。ひとつは血小板の効果を、二つ目は**トライアルにおけるこの製剤の安全性を、Dr Synderらによる SPRINT Trialにおける有害事象は2005年のTransfusionに掲載されている。**ここでもう一度、この論文の中にいくつかの表について着目したいと思う。最も強調したいのは表5である。ここでは両群において有意な有害事象についてまとめられている。**ここには両群において有意差のある11ケースまたは11タイプの有害事象について見ることができる。いずれの症状についても不活化群で有意に多く発生している。さらに点状出血、便潜血陽性、皮膚炎、発疹、胸膜炎、筋肉痙攣、肺炎、粘膜下出血と急性呼吸障害において不活化群で増加している。そしてこれ以外の有害事象についても臨床上 意義のある重篤なGrade3から4以上の有害事象として低カルシウム血症、意識消失、肺炎、急性呼吸障害の4つが挙がっている。**興味深いことにコントロール群ではこれらの有害事象はひとつもみられていないのである。**たと**

えば、ARDSについて言えば、不活化群318人のうち5人発症したのに対してコントロール群ではひとりも発症していない。意識消失についても同様で、不活化群で6人発症したのに対してコントロール群ではひとりもいない。低カルシウム血症については不活化群で20名に対してコントロール群で6人である。この文献の中でスポンサー達はARDSとされた患者の数名についてARDSと診断されたことが問題であると主張していて、この結果を持ち帰り、専門家による再解析を行っている。そして彼らは呼吸器イベントの数を見直したが最終的に再解析を行った結果、ARDSは依然として不活化群で12名、コントロール群で5名存在しており、はじめにあった統計学的有意差はなくなったもののARDSや急性呼吸障害といった問題は解決しなかった。

SPRINTスタディの有害事象データのまとめをする。両群間において9つのタイプの有害事象で統計学的な有意差を認めた。いずれも不活化群で有意に不利な結果であった。これらのうち4つの有害事象は臨床学的にGrade3または4であり、障害臓器は呼吸器、循環器、皮膚、副甲状腺ー腎臓（低カルシウム血症）である。**不活化処理を行った血小板に相関する可能性のあるリスクを考えると不活化血を受ける患者の60人に1人にGrade3から4の有害事象が発生することになる。**ここでベネフィット（利益）とリスク（損失）のバランスを考えてみよう。トライアルから得られたリスクは1/60であり、減らそうとしているリスクは1/150,000または1/75,000である。こういったタイプの解析に基づいて考えると、このタイプのリスクが現在のウイルスや細菌によるリスクを相殺するために処理製剤を広く使用することを正当化することは難しい。不活化の重要なコンセンプトのひとつに未知または新興感染症病原体の予防能力またはその可能性がある。もしもその病原体が世界中に蔓延して高い致死率をもたらすのであれば、不活化のベネフィットはそのリスクを凌駕するかもしれない。新興または現在活動性のある感染症に対して非常に弱い集団であれば、不活化のベネフィットはその集団にとってリスクを上回るかもしれない。

しかし、未知の感染症を見越して今から広く一般に不活化製剤を使用することは現在のリスク対ベネフィット比の議論から見て正当化することはできない。