

## 血液診断の新しい動き The Future of Hematological Diagnosis

21世紀を目前にした今、血液診断の将来動向について注目が集まっています。1999年11月6日、この分野の世界的権威である米国ウィリアム・バーモント病院のBruce Davis博士に、次なる世紀に必要な血液診断の検査項目、技術、そして装置の動向についてABX Diagnostic Inc.のRichard A. Sullivan社長が伺いました。博士は、まず既存の血球カウンタの高感化、直線性の改善について述べられ、続いて、急性炎症に反応する好中球によって作られる分子CD-64の測定に関する研究状況を紹介されました。特に、診断指標としてのCD-64定量分析の可能性について詳しく述べられました。さらに、免疫学的検査と血球計数を一体化した新たな検査装置、貧血症の自動フェリチン試験、そして病気の現状把握、抗生物質による治療効果の確認や血液透析患者のホルモン治療のための正確な投薬管理など、血液診断の将来について幅広く語っていただきました。



### **Bruce H. Davis, M.D.**

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*Dr. Davis is the author of more than 77 articles and book chapters, and 92 abstracts in the fields of hematology and cytometry. He has taught in medical schools in several states and lectured internationally. His research has earned him awards from the National Institutes of Health and the American Cancer Society, among many others. A member of 12 professional medical societies, he has practiced medicine since 1977.*

As the twentieth century closes, attention is focused on future trends in the field of hematological diagnosis. On November 6, 1999, Dr. Bruce Davis, Director of Analytical Cytometry at the William Beaumont Hospital and Mr. Richard A. Sullivan, President of Horiba Group's ABX Diagnostics, Inc. discussed their view of this future, including the testing parameters, technologies, and instruments that will be needed in the next century. Dr. Davis first describes a variety of desirable improvements to existing technologies including extending the low range and improving the linearity of platelet- and leukocyte-counting instruments. In the realm of developing and new technologies, Dr. Davis describes experimental work in measuring the elevated expression of CD-64, a molecule produced by neutrophils in response to acute inflammation. The potential for using quantitative CD-64 measurements as a diagnostic marker is detailed. The more distant future may see new instruments that combine blood counting with immunologic tests, an automated ferritin test for anemia, and instruments and methods that can accurately gauge the state of disease, the effectiveness of antibiotic therapy, and the exact dosage of hormone therapy for hemodialysis patients.

**Mr. Sullivan (R.S.)** Doctor Davis, what are the current trends in hematologic diagnosis in both testing parameters and instrumentation? Where do you see the market in the next five to ten years and beyond?

**DR. Davis (B.D.)** I think it's going to go in several areas. First, like any industry in medicine, evolution with new technology is going to occur in laboratory hematology. One area is going to be that of simply extending the range of linearity of the measurements we already do on the blood cell counters as well as improving the precision of the individual measurements. For instance, in the area of platelet counting, I think all of the instruments will continue to improve to make more accurate counts in the low range. This is important because of its relationship to therapeutic decisions on platelet transfusions. So I think the surviving and popular instruments are going to be the ones that accurately count platelets, certainly at 5000 and probably below.

**R.S.** What is the value of extending the range?

**B.D.** To extend it to the high end is probably not as critical from the point of view of therapeutics but is important from the point of view of laboratory work-flow and increasing the efficiency within the laboratory. It promises to decrease repeat testing and decrease the need to reflex to manual confirmatory testing, such as phase platelet counts, so that the value that comes from the instrument will be accepted with great assurance and there will be no need to further confirm it, since it will be well within the linearity range of the instrument.

**R.S.** One of our ABX products is used by the American Red Cross for plateletpheresis because the ABX instrument has an extended platelet range capability up to five million. Do you see that as a great value for that product?

**B.D.** Most certainly. Most hematology instruments fall down [when counting above] one million. We just don't have the linearity in these products where the platelet concentration is much higher, so for reasons of laboratory efficiency and productivity [ABX is] going to be an attractive alternative. The other area in terms of improving or extending the linearity and precision will be the leukocyte counting area, particularly neutrophils, because more and more with aggressive therapies, we see neutropenic in-patients recovering from bone marrow transplantation or undergoing aggressive chemotherapies for a number of malignancies. There again, the ability to reliably count to a low range means that the technologists have to spend less time reflexing to manual confirmatory methods so this will improve the work-flow and efficiency of the hematology laboratory staff.

**R.S.** Current instruments on the market, including ABX, do flag nucleated red cells, but you're indicating that a quantification is more important.

**R.S.** デービス博士,最近,血液診断の検査項目と装置の動向はどのようになっていますか? また,5年,10年先の市場状況を先生はどのように見ておられますか?

**B.D.** 他の医薬品業界と同じように,血液臨床検査の分野でも技術革新が起っています。一つは血球カウンターの測定レンジの拡張です。例えば,血小板では,より低濃度領域をより高精度でカウントする装置への改善が進んでいます。これは,血小板輸血の治療的判断に関係するので特に重要です。

**R.S.** レンジ拡張はどこまで進むのでしょうか?

**B.D.** 高濃度側に拡張することは,診療学的な見地よりむしろ,臨床検査の効率を上げるために必要です。測定範囲の直線性を広げることにより,再検査や的手法による確認テストを減らし,測定結果の信頼性向上に役立ちます。

**R.S.** ABXの製品が血小板を最大5百万までカウント可能なことから,アメリカ赤十字で血小板の泳動測定に使われています。この値は高いと思われませんか?

**B.D.** もちろんです。他の装置の殆どが百万以下です。この種の装置は,濃度の高い領域での直線性を保つことは難しく,臨床検査の効率を上げる意味からもABXの製品は魅力的です。

**B.D.** Right. I think that certainly with the high-end instruments, for the complex hematology laboratory, the ability to count nucleated red cells, or at least sensitively detect their presence, will be a useful parameter. We are already seeing some companies in the field having instruments that count what I would consider actually a fairly high level, but I think that's going to be extended to a low level.

**R.S.** What new and exciting products have you seen recently?

**B.D.** I think in the last few years we've seen the ability to add on new parameters for cells that are useful in hematology diagnosis. In the area of reticulocytes, the increased accuracy and the ability to measure other parameters by using fluorescent dyes such as thiazole orange, the same dye that's on the ABX Pentra 120 Retic instruments can be not only more accurate in its counting reticulocytes and much more labor-efficient but also create new ways to look into the erythrocyte or erythropoietic response. Here I'm referring to the ability to measure the more immature fraction of the reticulocytes what we now call the immature reticulocyte fraction parameter.

The IRF parameter, which is available as an FDA-approved parameter on the Pentra 120 Retic instrument [is] very useful in following patients with a number of anemias whether it be for the purpose of classifying anemias or following the therapeutic response during the treatment of anemias from common disorders such as iron deficiency (to validate that there is a response to the iron replacement therapy), or in more complex clinical conditions like following the engraftment of [a patient after] bone marrow transplantation. So that's one parameter that I think made a real contribution to health care through laboratory hematology testing. I've already mentioned the ability to count nucleated red cells, so that's another area. I think we're now beginning to see several companies develop and get into alternate ways to look at the platelet counting area and even get into ways to look at the bone marrow response to thrombocytopenic conditions. We've mentioned previously the need to count more accurately the lower levels and [there are] some instruments around the field now with the ability to use immunologic methods to count platelets accurately, or at least use immunologic methods to validate the accuracy of their technology to count platelets.

**R.S.** On a specific platelet count, wouldn't that be more costly than the current technology?

**B.D.** Yes. What I'm referring to [is one of ABX's competitors] has come out with an immunoplatelet count using what we call CD-61, a platelet-related antigen, to more accurately determine whether the small particles counted through the platelet aperture are indeed platelets. And, interestingly, I think these studies with this method, parallel what I anticipate to be the new reference method for platelet counting-so-called «immunoplatelet ratio» counting using flow cytometers. It seemingly shows actually how good optical and even impedance platelet counting can be. So, whether that sort of product will ever [be commercial], I have my doubts.

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直線性と測定精度の向上のもう一つの効用は、白血球、とくに好中球のカウントです。このパラメータは、骨髄移植や化学療法の有効性確認などに有用です。低濃度領域における信頼性の向上は用手法による照合を省け 検査室の効率アップにつながります。

**R.S.** 有核赤血球診断装置では定量性の高さがより重要になってきていますね。

**B.D.** その通りです。複合的な血液検査を行う上級機種では、有核赤血球を測れる 少なくとも 検出できることは非常に有効です。

**R.S.** 最近 新規でわくわくするような製品をご覧になりましたか？

**B.D.** ここ2~3年、血液診断の際に有用な情報を含む 細胞診断が可能なものが現れてきています。チアゾールオレンジなどの蛍光染料を用いて、網赤血球をより正確に測ることができる装置、ABXのPentra-120 Reticなどがそうですね。

Pentra-120 Reticが持つ検査項目の一つであるIRFという成熟度指数は、鉄欠乏症の診断や血小板減少症に関連した骨髄移植患者の診断に有効です。なお、IRFは米国食品医薬品局(FDA)でも認められた指数です。

この他、幾つかの会社が試みている低濃度の血小板を免疫学的な手法で計数する装置なども有用でしょう。

**R.S.** We understand you're currently working on a research project with ABX on CD-64.

**B.D.** That's right. My laboratory has been interested in this molecule for probably eight years now, because we had an early recognition that in a way it's unique in terms of being a potential diagnostic marker where, although there are many antigens that change on the neutrophil of myeloid, it's unique because its expression is very low in the normal state and then becomes high. So, from a diagnostic point of view, you go from a single signal that is nothing to something [very noticeable]. The level or quantitative increase really correlates with the degree of the inflammatory reaction within an individual. So we see it as a first time ability to contribute to infectious disease and the detection of potential infections. So we've been very excited about the work with ABX we're doing because we believe we'll be able to develop this parameter on a hematology instrument and probably be the first manufacturer to do so.

**R.S.** Are there any other parameters in the hematology field that are of great interest but that cannot be measured today?

**B.D.** I think beyond CD-64, [there has been quite a bit of research interest in] reticulated platelets. Higher levels or percentages of reticulated platelets correlate with an increased drive of platelet production or active thrombopoiesis. And here again with this same dye, thiazole orange, which is on the existing ABX Pentra-120, this too can be used to measure reticulated platelets.

**R.S.** You mentioned combining an immunological technique to a hematology parameter. Horiba, our parent corporation in Japan, has recently developed a combination hematology and immunology parameter system including normal CBC parameters and a CRP assay. Do you see that as of major interest and clinical significance?

**B.D.** I do. I think although it certainly breaks down the walls, if you will, and the barriers of the traditional separation of immunology or chemistry labs from the hematology labs from a testing point of view, it really makes a lot of sense, particularly in the physician's office. Let's take for example the rheumatologist, the two basic needs are to make sure the patient is not anemic or has neutropenia, and to monitor the immunologic side of their disease. [This] is commonly either through sedimentation rate or CRP measurements. So that can be, I think, a very valuable combination to certain subsets of physician offices. It will make patient treatment much easier and much more real-time for the physician to know what the CRP is, what is their anemia, and have the answer right there.

**R.S.** What other tests would you see that would be immediately valuable to add to this Horiba CRP line. If we had the capability what other tests would you like to see that make sense to combine with hematology.

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**R.S.** 特殊な血小板を測ることは 検査費用が高つくませんか？

**B.D.** いいえ。ご紹介する方法は CD-61と呼ばれる血小板に関連した抗原を用いたアパーチャ・インピーダンス法による免疫学的な血小板カウント手法で、いわば、真の血小板計数方法です。この手法は、フローサイトメータを使って免疫的血小板比率と呼ばれる新しい血小板計数の参照法になり得るものと期待されており、より経済的であるとも言えるのです。

**R.S.** 先生はABXのCD-64研究プロジェクトにも関わっていらっしゃいますね。

**B.D.** その通りです。我々の研究室では、当初よりこの分子の感染症診断用指標としての能力に着目し、8年に亘って研究を続けています。ABXと一緒にあって精力的に研究を続けているので、この診断項目を組み込んだ血液診断装置を最初に完成させることができると信じています。

**R.S.** この他、血液診断の分野で、非常に興味深いのが現在は測ることができない指標はありませんか？

**B.D.** CD-64以外では、細網血小板でしょう。そのレベルが高いと、血小板減少症に関係しています。試薬は Pentra-120で採用しているチアゾールオレンジを使います。

**B.D.** I think the next logical one, aside from inflammatory disease detection, is further work on anemia. The most common anemia, worldwide, is iron deficiency. So why not CBC plus ferritin. At the moment ferritin is clearly the best single marker for iron deficiency [perhaps] do an immunologic assay for that.

**R.S.** What do you see the worldwide market demanding. Are the demands similar around the world or different in each country and if it is different, why?

**B.D.** Well, I think currently there still are regional differences, but those borders are really coming down [because of] increasing the cross-fertilization of ideas through manufacturers, through medical conventions, whatever. I think we are seeing things becoming more alike rather than dissimilar. But, clearly, there still are some regional differences. For instance it was not that long ago that I was surprised to learn in the United States the reticulocyte assays run probably less than five percent of the time in relationship to a CBC, whereas in Japan and other countries, a few in Europe, it was kind of a standard test. So instead of a CBC being the standard evaluation by a physician, it would be a CBC and «retic.» And certainly in Europe and Japan they use the CRP much more than in the United States where the sedimentation rate is still held onto as a monitor. So in terms of laboratory testing I do think that there [will be] more similarities than dissimilarities as the art of medicine becomes more scientific and less parochial in its approach.

At the most recent ISLH meeting which was in Kobe Japan in September of 1999, we had a panel discussion with representation from all areas of the world, where they were asking the common question of what was the impact of both regulatory issues as well as fiscal issues, whether it be managed care, whether it be decreased funding of a national health care system. We really discovered we had a lot more in common than dissimilar, that we were all as laboratorians under increasing pressure to become more efficient and be more economical and justifying the clinical utility of what we do as well as also being under increased regulatory scrutiny.

**R.S.** Can you elaborate on the notion of «being more economical?»

**B.D.** I think we have that potential, particularly with some of the newer parameters. For instance the IRF parameter that is on the Pentra 120. We have finished the study and are now analyzing the data where we think that parameter can provide objective information on a certain subset of patients, the patients on renal dialysis receiving recombinant erythropoietin therapy. Now that, in any country, is an expensive drug, it's thousands of dollars a year. And yet there really isn't a good indicator of what dosage is necessary. And it's a drug, a hormone that drives erythroid production to raise the blood count and the IRF should be a very useful parameter to provide earlier indication what the impact of this drug therapy is. So that, I think, is an example where good laboratory testing can be used to parlay the influence on pharmacologic agents that are very expensive.

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**R.S.** 先程、免疫学的技術を血液診断指標に加えることについて言及されましたね。我々の親会社である日本のホリバが、血球検査とCRP検査の二つの機能を一台の装置に組み込んだ小型の検査装置を最近完成させました。先生は、この装置が、大きな関心を呼び、また、診断上重要だと思われませんか？

**B.D.** もちろんです。ポイント・オブ・ケアの観点からしても、従来の臨床検査室で見られるような化学的検査法と免疫学的検査法との間にある壁を取り払うことは大いに意味のあることです。臨床的には、例えば、医者がリュウマチ患者をリアルタイムで診断を下すときに効力を発揮します。

**R.S.** この製品に追加して、すぐに役に立つような診断項目は他にありませんか？

**B.D.** 感染症の次は貧血でしょう。全世界的に最もポピュラーな貧血は鉄欠乏性貧血です。鉄欠乏症の診断マーカとしてはフェリチンを加えることが賢明でしょう。

**R.S.** 血液診断の市場を世界的に見た場合、要求は各国同じでしょうか？ それとも国毎に異なるのでしょうか？

**B.D.** 今のところは多少違いますが、境界は徐々になくなりつつあります。例えば、網赤血球検査は、アメリカでは全血検査よりも5%も少なくなっていますが、日本やヨーロッパのいくつかの国では標準的な検査項目です。

Similarly with the CD-64 testing of the patient with infection. With sepsis detection, we think that could be very useful in not only identifying the individuals that require therapy and might require more intensive healthcare utilization such as a triage role of somebody coming into the emergency room or seeing a physician and the concern is: «does this patient have a severe infection?» Or, in the modern arena of patients being treated by antibiotics, to answer the question is this patient sufficiently under control with regard to the infection that the antibiotic coverage can either be changed so that it becomes say from a triple IV antibiotic use to an oral use and early discharge from the hospital, or simply shortening the amount of antibiotics. Not only from the point of view of better treatment of the patients is this important, but also from reduction of the increasing healthcare problem of antibiotic-resistant organisms. The only way that's going to be ameliorated in the future is to reduce usage of antibiotics. Well we need a test to provide the treating clinician, the infectious disease person with the confidence that antibiotics are either not necessary or they've done their job and don't need to be continued for another week.

**R.S.** As a full-service organization, the Horiba Group is focused on customer satisfaction: on-time delivery, a quality product, low downtime, etc. Do you see the next logical step for customer satisfaction is an ability to do diagnostics on instrumentation from a remote location?.

**B.D.** I think it certainly makes a lot of sense. I believe that using communication technology can be both more accurate and more cost-effective. If we can use the internet and use modems to interact with an instrument from a remote site. From the ABX service center you can have one person doing the diagnostics or some routine on hundreds of instruments in a day. You can't have a service person visiting one hundred accounts in a day. So I think it really does make a lot of sense in terms of better service and reducing costs all around.

**R.S.** Recently we talked about a three-part differential instrument developing into a five-part or even a five-plus-part differential instrument. Almost all of the current manufacturers have at least a three-part differential. Do you see a five-part differential more diagnostically positive for diagnosis or is there a big advantage of having a low-cost five-part differential over a low-cost three-part differential.

**B.D.** I think that the short answer is yes, because clearly it's a more accurate measure. There are five basic types of leukocytes circulating in the blood. To only count three of them is really only doing part of the job. Now one could argue that it's not important for every patient at every time, but I think that if you're asking for a complete blood count, you should get a complete blood count. Certainly in some clinical disease states knowing what the eosinophil level is or the presence of basophilia can be important, not to mention that quantifying those other two cell types more accurately means that your neutrophil count is the accurate neutrophil count-very important!

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1999年9月に日本の神戸で開かれたISLH会議では、診断項目のあるべき姿と、同時に医療費をいかに削減するかとの議論も盛んに行われました。精密検査が増えるなかで、医療費をどのように効率的に活用するかは、各国共通の課題であるとわかりました。

**R.S.** “さらに経済的に”ということについては、いかがでしょうか？

**B.D.** 新しいパラメータを導入すれば可能だろうと考えています。例えば Pentra-120のIRFという新しいパラメータを用いることにより可能です。我々は、組替え型の赤血球増進治療を受けるような腎臓透析患者の診断に有効な項目を見出しました。治療薬の使用量について、IRFは有効な指標になります。高価な薬剤を有効に使うときに、臨床検査が役立つ例です。敗血症の診断にも有効です。負傷兵の分類や患者の重篤度を判断したり、アレナウィールスに対する抗生物質の投与の判断にも有効です。

**R.S.** ホリバグループは、総力を結集して顧客満足度の向上を目指しています。具体的には、素早い対応、高品質の製品、故障によるムダ時間の排除などです。リモートメンテナンスは如何でしょうか？

**B.D.** 本当に重要だと思います。通信手段をうまく使うことは、より正確で、よりコストのかからない検査につながります。インターネットを介らせて検査室とサービスセンターをつなぐことにより、一人の人間が一日に百件もの装置をサービスすることができます。

**R.S.** In the past, analyzers didn't provide a five-part differential because it's costly. But the advancement in recent technologies, specifically ABX's enables us to have a low-cost five-part differential.

**B.D.** I believe that now the availability of the Pentra 60 in the U.S. market is going to be a real plus for clinicians as well as for ABX.

**R.S.** Do you have any specific message you'd like to give to the readers as far as your final assessment on the future of hematology?

**B.D.** I think for those people in laboratory hematology that don't know ABX, watch out, because you will shortly.

**R.S.** Doctor Davis thank you.

**B.D.** It's a pleasure.

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**R.S.** 最近の血球装置は、少なくとも3分類を備えていますが、5分類あるいはそれ以上が必要でしょうか？

**B.D.** 端的に言えば必要です。白血球には基本的に5つのタイプがあります。3分類は、部分的な仕事でしかありません。特に、ある種の患者では好酸球のレベルと好塩基球の存在を調べることは非常に重要です。

**R.S.** 従来5分類は高価なものでしたが、最近の技術革新により特にABXでは安く提供できるようになりました。

**B.D.** 私もABXのPentra-60は米国市場でもきっと歓迎されると思います。

**R.S.** 最後になりましたが、何か血液検査の将来について付け加えていただくことはありませんか？

**B.D.** 今はABXと言う名前をご存じない血液検査室の皆様には是非ABXに注目していただきたいですね。まもなくそうなるとは思いますが。

**R.S.** デービス博士、ありがとうございました。

(抄訳 編集部)