GALLERY ARTICLE

A Picture is Worth a Thousand Words

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INTRODUCTION

During the past forty years blood cell analysers have developed from comparatively simple semi-automated single parameter devices producing only numerical data to fully automated complex multiparameter devices frequently employing multiple technologies and producing a bewildering array of numerical and graphical parameters. The history of these developments is well described in a text by Groner and Simson[1] in 1995. In spite of these developments, however, many laboratories continue to ignore all but the numerical output of analyzers, which they report to the clinician frequently as uninterpreted data. Raw data often has minimal or no information content. For many, routine analytical haematology remains locked into a time frame defined by Wintrobe in the 1930s[2]. Modern cell counters, however, provide significant additional information, some of which overlaps that obtained at the microscope and some that is undoubtedly new. The latter possesses the capability to improve patient care both in a diagnostic and in a therapy monitoring sense. Ignoring these new parameters including the graphics is tantamount to 'throwing the baby out with the bath water', which seems to be a bad practice. At least six companies now produce multiparameter haematology analysers but employ various often subtly different methods and reagents for identifying and classifying cells. As a result a series of instrument specific parameters is produced and for correct clinical interpretation the particular method used must be known. The principles of measurement employed in haematology analysers manufactured by the Sysmex Corporation have recently been reviewed by Fujimoto[3].

This is the first of a series of articles describing the graphical output of the Sysmex XE-2100 and illustrating examples of clinical benefit following the scrutiny and analysis of scattergrams. The clinical cases illustrated come from a variety of sources within Europe and Sysmex is very grateful to the many clinicians who have given permission for their publication. A detailed description of these cases together with others is available and can be found on the Sysmex Europe homepage.
http://www.sysmex-europe.com/caseforum/
A new case contribution is submitted every month.

EXAMPLES OF NORMAL AND ABNORMAL SCATTERGRAMS

The XE-2100 generates six different scattergrams including DIFF scattergram, WBC/BASO (white blood cell/basophil) scattergram, IMI (immature information) scattergram, NRBC (nucleated red blood cell) scattergram, RET (reticulocyte) scattergram, PLT-O (optical platelet) scattergram. In addition there are RBC and PLT-I (impedance platelet) histograms[4].

For the WBC 4-part differential the reagent subsystem lyses RBCs and acts on WBC membranes to allow dye entry to stain DNA and RNA within the cells. The sample is then analysed by flow cytometry using a semiconductor laser to detect side fluorescence and side scattered light from which the DIFF scattergram is generated (***Figs 1 and 2***).

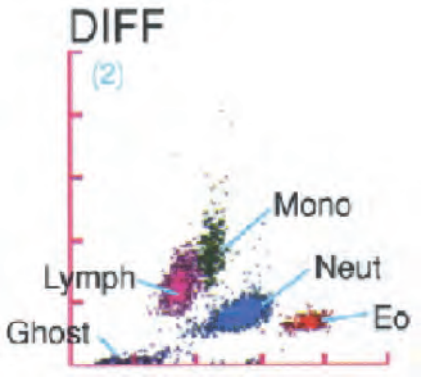

Fig. 1 *Normal DIFF scattergram*

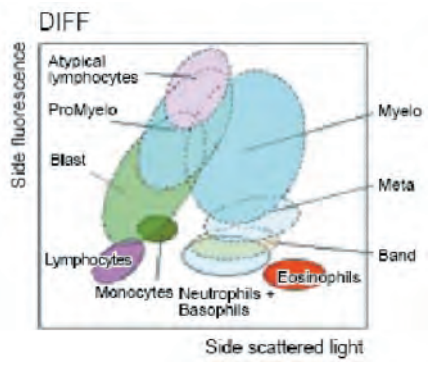

Fig. 2 *Abnormal DIFF patterns (schematic)*

For measurement of WBC/BASO the reagent subsystem lyses the RBCs and selectively suppresses degranulation of basophils resulting in their separation from other forms of WBC. After this reaction the sample is analysed by flow cytometry using a semiconductor laser to detect forward and side scattered light information (***Figs 3 and 4***) from which the WBC/BASO scattergram is generated.

For measurement in the IMI channel a polyoxyethylene series non-ionic surfactant and a sulphur-containing amino acid lyses mature WBCs. Immature cells of the granulocyte series are protected by the amino acid against lysing. The IMI scattergram is based on DC and RF impedance signals (***Figs 5 and 6***). Further qualitative differentiation of immature cells of the granulocyte series in the IMI channel is possible. The effect of the lysing reagent differs with each type of immature cell. Mature WBCs are, however, completely shrunken and located in the ghost area of the scattergram.

The XE-2100 counts reticulocytes and platelets using forward scattered light and side fluorescence (***Figs 7 and 8***). The fluorescent dye contains two stains, polymethine and oxazine. These two dyes penetrate the cell membranes staining RNA in reticulocytes and DNA/RNA in nucleated cells. Reticulocytes are separated from mature red cells by the differences in RNA content and from nucleated cells by differences in DNA/RNA content. By analysing the RET scattergram, reticulocyte counts, reticulocyte ratios for individual reticulocyte fluorescence intensity zones (LFR, MFR, HFR), immature reticulocyte fraction (IRF) [***Figs 7 and 8***] and optical platelet count [***Figs 9 and 10***] are determined.

The XE-2100 counts NRBC using side fluorescence and forward scattered light (***Figs 11 and 12***). The reagent subsystem causes lysis of mature RBCs and exposes NRBC nuclei. The specific dye stains WBC intracytoplasmic organelles and nuclei quite strongly while the staining of the NRBC nuclei is comparatively weak allowing clear discrimination of the two types and making NRBC counting possible.

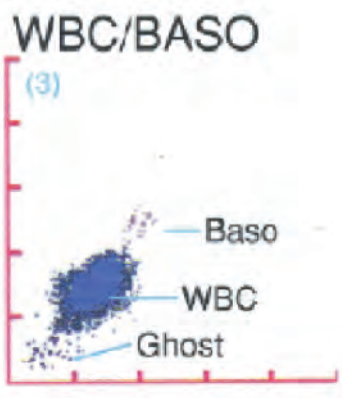

Fig. 3 *Normal WBC/BASO scattergram*

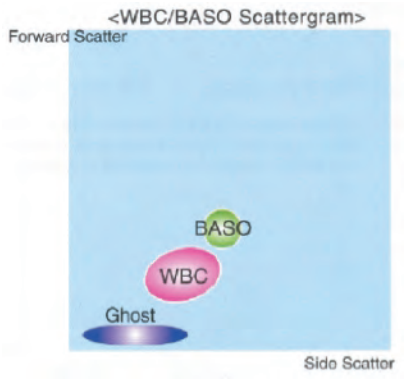

Fig. 4 *WBC/BASO patterns (schematic)*

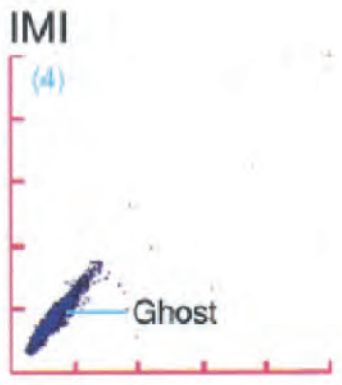

Fig. 5 *Normal IMI scattergram*

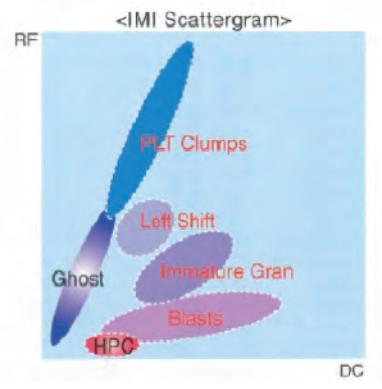

Fig. 6 *Abnormal IMI patterns (schematic)*

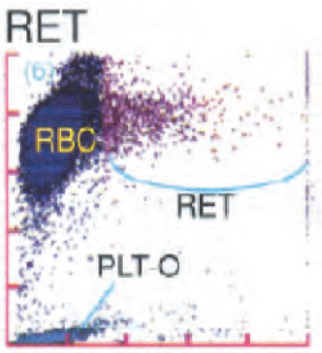

Fig. 7 *Normal reticulocyte scattergram*

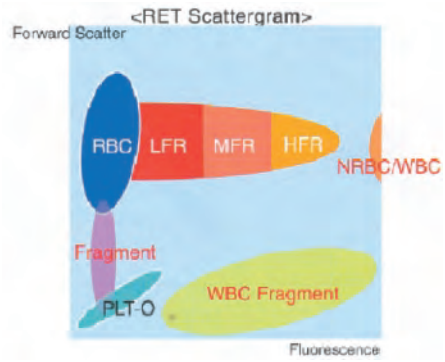

Fig. 8 *Abnormal reticulocyte patterns (schematic)*

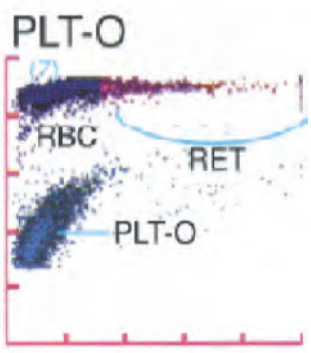

Fig. 9 *Optical platelet (PLT-O) scattergram*

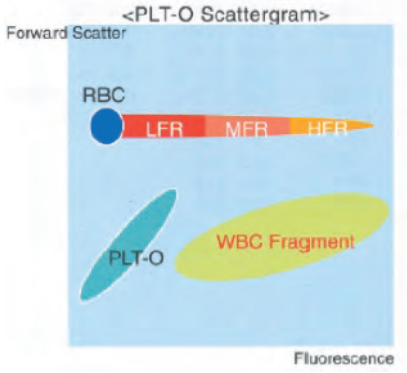

Fig. 10 *Abnormal PLT-O patterns (schematic)*

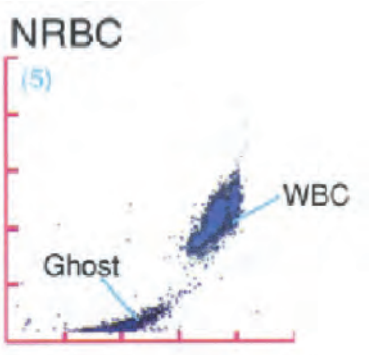

Fig. 11 *Normal NRBC scattergram*

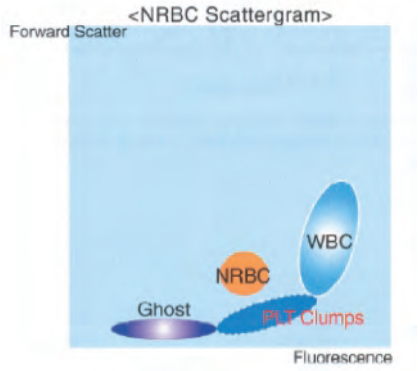

Fig. 12 *Abnormal NRBC patterns (schematic)*

THE SYSMEX INFORMATION SYSTEM (SIS)

Those interested in learning more about the Sysmex Information System (SIS) are referred to the following article in this issue of the Sysmex Journal International pp. 7-12 "Comparision of Technical Validation before and after Implementation of the Work Area Manager SIS 2.0 with Standard Rule Package" by A. Jenny, F. Senn, J. Wey, M. Tschopp, W. A. Wuillemin, J. Linssen / Switzerland, Germany.

ACUTE MONOCYTIC LEUKAEMIA (FAB-M5b)

This case illustrates the value of the XE-2100 in detecting acute monocytic leukaemia (AM_OL) and in differentiating between mature and immature monocytic cells.

The patient is a 68-year-old female who presented with anaemia, thrombocytopenia and an extremly elevated WBC count (***Fig. 13***).

The peripheral blood smear showed a spectrum of cells with monocytoid features ranging from large undifferentiated blast cells with abundant poorly granular vacuolated basophilic cytoplasm (22%) to more differentiated cells with the features of promonocytes and monocytes (58%). The monoblasts are characterized by large nuclei with delicate lacy chromatin, and up to three large vesicular nucleoli (***Fig. 14***). The cytoplasm is basophilic and voluminous and often shows one or more pseudopodia. The promonocyte illustrated in ***Fig. 15*** is similar to the monoblast but has a large nucleus with a cerebriform appearance; nucleoli are present, but the cytoplasm is less basophilic, has a greyish ground-glass appearance, and often has fine azurophilic granules (but not in the present example). Mature monocytes are illustrated in ***Fig. 16***.

These microscopy appearances suggested a diagnosis of acute monocytic leukaemia type M5b in the FAB classification, which was subsequently confirmed by cytochemical staining (myeloperoxidase (MPO) and non-specific esterase (NSE) stain were positive) and immunophenotypic analysis (CD13+; CD33+, CD65+; CD15+; CD14+; CD4dim+; CD64+; CD56+; CD11a+; CD2+ and HLA-DR+ [CD117; CD34 only 7% positive]).

Returning to the initial haemogram (***Fig. 13***), note that the "Blasts?" flag is generated. This is because cells are present in the blast cell areas of both the DIFF scattergram and the IMI scattergram indicating that these are of myeloblast/monoblast lineage rather than lymphoblast. The DIFF scattergram shows a large abnormal monocyte population, while the IMI scattergram shows that the majority of these abnormal cells are immature precusor cells with large volume (DC) and high nuclear/cytoplasmic ratio (RF). The latter are monoblasts and perhaps promonocytes although this is difficult to establish unequivocally.

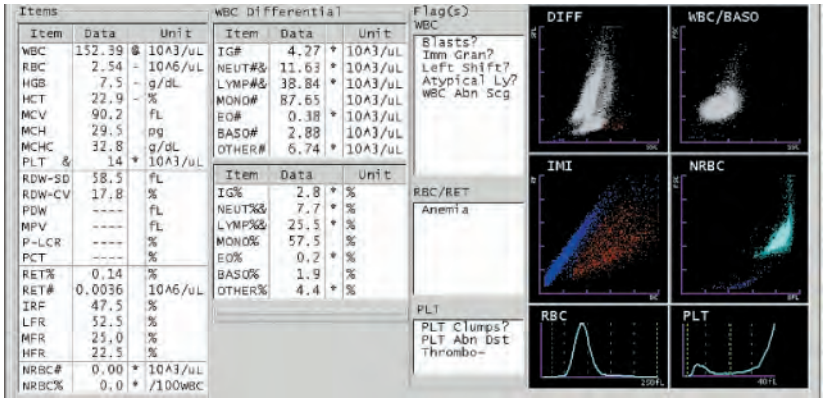

Fig. 13 *Presenting haemogram showing anaemia, thrombocytopenia and leukocytosis*

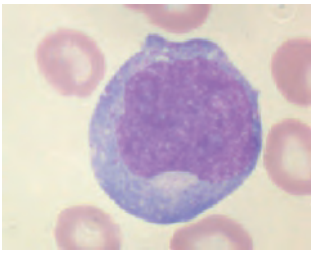

Fig. 14 *Monoblast*

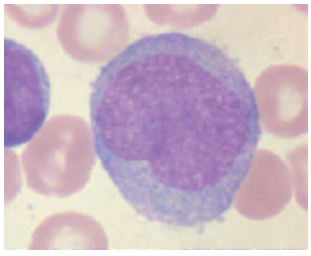

Fig. 15 *Promonocyte*

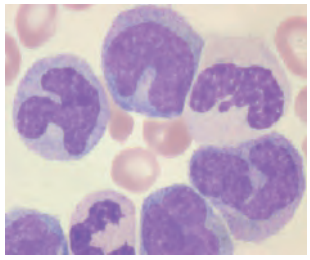

Fig. 16 *Mature monocytes*

The presence and positioning of the red dots in the IMI scattergram may be an important differential diagnostic characteristic. It has already been established that lymphoblasts do not appear in the IMI scattergram. Three IMI patterns are illustrated below (***Figs 17, 18 and 19***).

The IMI scattergram depicted in ***Fig. 17*** shows an immature population (red dots) with a proportion of high volume cells (DC x-axis) and a high nuclear/cytoplasmic ratio (RF y-axis) suggesting differentiation characteristics of promonocytes. ***Fig. 18*** is from a patient with chronic myelomonocytic leukaemia with a differential leukocyte count containing 60% mature monocytes and a virtually empty IMI channel. ***Fig. 19*** is from a patient with AML-M2 whose peripheral blood contained more then 20% small blasts and only a few differentiation characteristics.

Classified as monocytic or M5 in the FAB system, two subtypes exist namely M5a (acute monoblastic leukaemia without maturation) and M5b (acute monoblastic leukaemia with differentiation or acute monocytic leukaemia). In the new WHO classification these disorders fall into subgroup 4-AML not otherwise categorised, therefore the diagnostic characteristics of the FAB system are retained. Subtyping depends mainly on morphologic examination of the marrow and estimation of the % of monoblasts versus more mature monocytic cells, namely promonocytes and monocytes. The present case illustrates yet another differential diagnostic capability of the XE-2100.

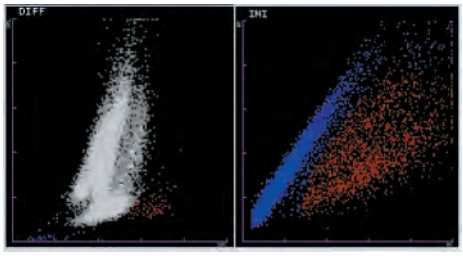

Fig. 17 *Present case. Acute monocytic leukaemia (AML-M5b)*

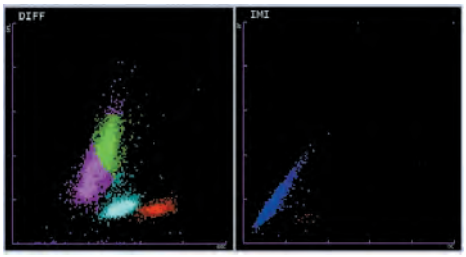

Fig. 18 *Chronic myelomonocytic leukaemia (CMM_oL)*

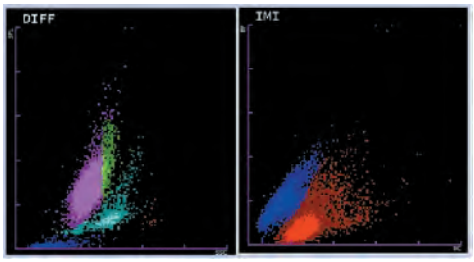

Fig. 19 *Acute myeloblastic leukaemia (AML-M2)*

XE-2100 : PLATELET COUNTING

The XE-2100 incorporates two state-of-the-art platelet methodologies, impedance (PLT-I) and fluorescent optical (PLT-O), to assure accurate and reliable platelet counts. The ability to perform platelet counts by these two different technologies presents the opportunity to provide more accurate platelet information. The analyser always provides an impedance count but there is an optical fluorescent count available when run in reticulocyte mode. RBCs and PLT-I are counted in the RBC/PLT channel using the hydrodynamically focused direct current (DC) detection method. The DC detection method of platelet counting allows increased accuracy because of the large number of particles that can be counted. However, it is well known that in specimens where small RBCs or large platelets are present, accuracy may be decreased because of overlapping populations. In such specimens, the PLT-O measurement can provide a more accurate platelet count because overlapping of populations is avoided. Reticulocytes and PLT-O are counted by flow cytometry in the RET channel using a semiconductor laser and a nucleic acid fluorescent (polymethine) dye and analyzing both forward-scattered light and side fluorescence information. A switching algorithm is incorporated within the analyser software to report the most 'correct' platelet count, either optical or impedance. In samples containing extremely microcytic or fragmented erythrocytes or giant platelets, the platelet distribution curve is abnormal and the optical count is reported. When white cell fragments are present (not uncommon in patients receiving chemotherapy) these are included in the optical platelet count, a "platelet abnormal scattergram" flag is generated and the impedance count is reported.

In many routine laboratories it has been assumed that the optical method gives the most accurate platelet count at low levels and for this reason the switching algorithm has been over-ridden. A study reported by Briggs, Kunka and Machin (2003)[5] strongly refutes this practice. In this study, more than 500 cytotoxic chemotherapy samples from patients with haematological malignancies and platelet counts less than 20×10^9 /L in reticulocyte mode were selected and impedance, optical and reported (selected by the switching algorithm) counts were compared to the international reference flow cytometric method (Harrison, *et al*. 2001)[6]. For chemotherapy samples in the majority of cases the impedance count proved to be the most accurate and was the most frequently reported result by the analyser. Of the remaining samples when the switching algorithm selected the optical count then this count was the most accurate. Overriding the switching algorithm and always reporting the optical count will clearly not give the best platelet count. In a number of cases the counts would be falsely high and could result in patients being denied platelet transfusions when indicated.

ESSENTIAL THROMBOCYTHAEMIA

- an example of platelet under-counting by impedance

The patient is a 52-year-old female admitted to hospital with pulmonary embolism. Splenomegaly was noted. The initial XE-2100 haemogram (***Fig. 20***) showed an elevated impedance PLT count of 1,502 × 10^9 /L with mild normochromic, normocytic anaemia, a normal leukocyte count, but with 1% immature granulocytes. Peripheral blood film examination confirmed the thrombocytosis with many giant platelets (15%) and some (< 1%) megakaryocyte fragments (***Fig. 21***). Numerous Howell-Jolly bodies were present resulting from splenic dysfunction. The bone marrow showed marked megakaryocytic hyperplasia (***Fig. 22***). A diagnosis of essential thrombocythaemia was made.

The presence of giant platelets is the reason for the difference between the hydrodynamically focused underestimated impedance platelet count (PLT-I = 1,502 × 10^9/L) and the correct optical fluorescence stained platelet count (PLT-O =2,114 × 10^9/L) on the XE-2100 (***Fig. 23***). There is no overlap between giant PLT and RBC of similar size following RNA staining.

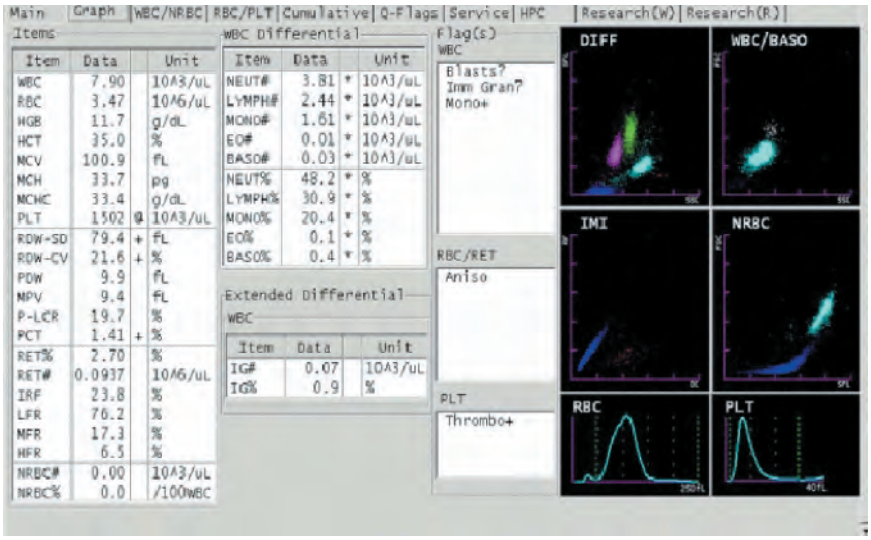

Fig. 20 *Presenting haemogram. Note the impedance platelet count is 1,502×10^9 /L*

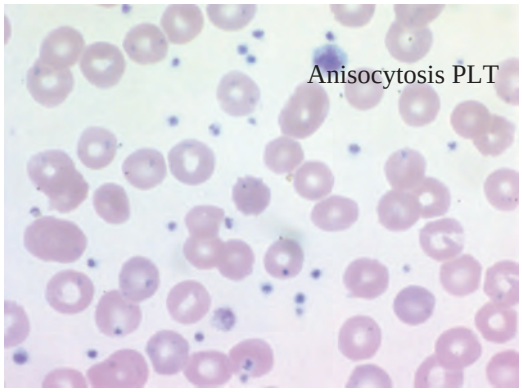

Fig. 21 *Peripheral blood film with thrombocytosis and giant platelets*

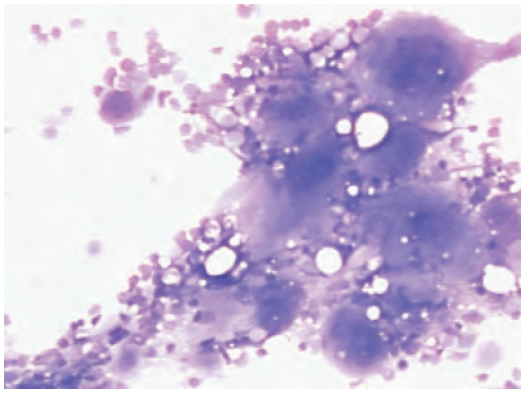

Fig. 22 *Bone marrow showing megakaryocytic hyperplasia*

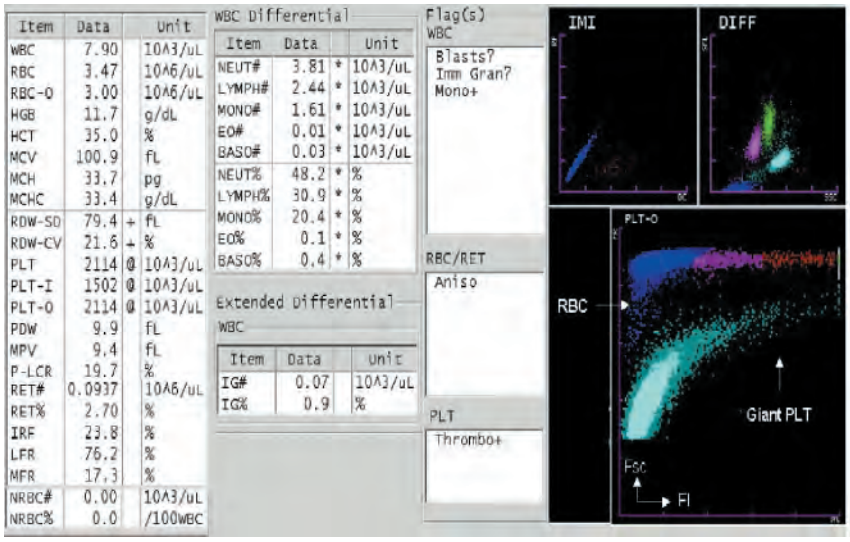

Fig. 23 *XE-2100 haemogram (RET mode)*
Note the difference between the impedance and optical platelet counts.

MULTIPLE MYELOMA

The patient is a 67-year-old male suffering from Bence Jones (λ) multiple myeloma with extensive infiltration of the bone marrow and osteoporosis. Immunophenotypic analysis showed expression of CD38, CD138, CD56, cyIgM and cy λ but no expression of CD10 and CD34/CD33. This indicates that the malignant cells are mature with B-cell activation (CD38, see ***Fig.24***) and L-chain λ (Bence-Jones protein).

Further laboratory data shows elevated levels for serum calcium (13.1mg/dL) and serum creatinine (2.9mg/dL). Bence-Jones protein excretion was grossly elevated (14g/24h).

The presenting XE-2100 haemogram is illustrated in ***Fig. 25*** and reveals a pancytopenia (Hb 89g/L, total leukocyte count 1.86×10^9 /L, PLT-I 19×10^9 /L). The reticulocyte count is 0.6% and the HFR (high fluorescence reticulocytes) fraction is 0% indicating failure of erythropoiesis presumably due to bone marrow infiltration by myeloma cells.

The DIFF scattergram of the XE-2100 depicted in ***Fig. 25*** shows essentially a single population of cells restricted to the lymphocyte region but exhibiting very high fluorescence activity. (Total lymphocytes are Lymph% 45.4 + "other" 46.8% = 92.2% see enlarged DIFF scattergram in ***Fig. 26***).

Examination of the peripheral blood smear shows a single population (90%) consisting mainly of mature small plasma cells (confirmed by immunophenotyping see ***Fig. 24***). This suggests that the fluorescence staining does not only give information about the size of the nucleus (DNA), but also about activity in the cell cytoplasm (RNA in the ribosomes).

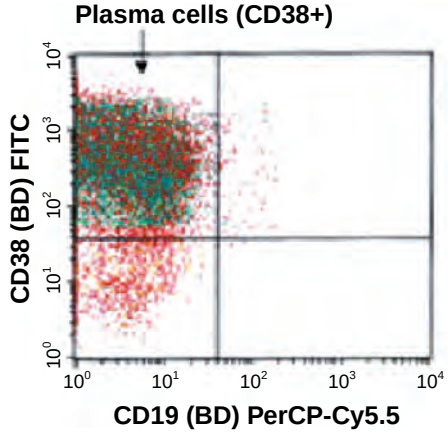

Fig. 24 *Immunophenotypic analysis (Becton Dickinson)*

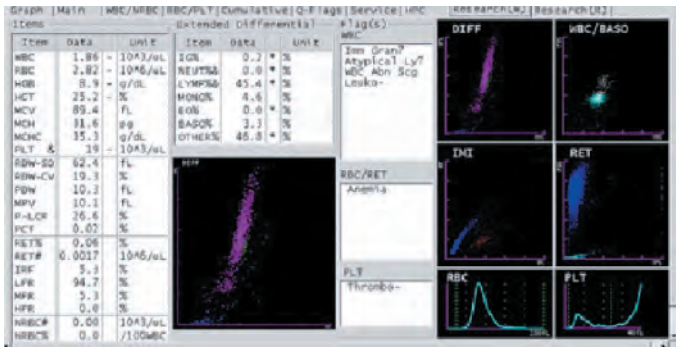

Fig. 25 *Pancytopenia in a patient with multiple myeloma*

The IMI (***Fig. 27***) and DIFF scattergrams show < 1% immature cells confirmed on peripheral blood smear examination (1% metamyelocyte). The combined interpretation of the DIFF and IMI scattergrams depicted in ***Figs 26 and 27*** shows that the population in the DIFF-channel are lymphoid cells with a high DNA/RNA content but that such cells are not represented in the IMI channel (all mature cells).

The peripheral blood smear shows RBC rouleaux (***Fig. 28***) caused by the high protein concentration and mature small plasma cells (***Fig. 29***).

An important criterion for the WHO classification of Bence-Jones myeloma is a plasma cell bone marrow infiltration greater than 30%. ***Fig. 30*** shows an XE-2100 profile obtained from an essentially pure culture of plasma cells. The DIFF scattergram is very similar to that of the patient's peripheral blood.

This was confirmed microscopically on the bone marrow smear (***Fig. 31***), which showed > 80% mature plasma cells.

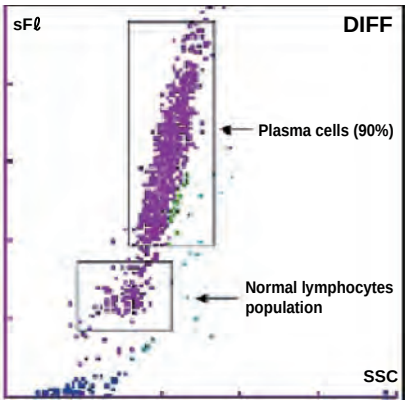

Fig. 26 *Enlarged DIFF scattergram*

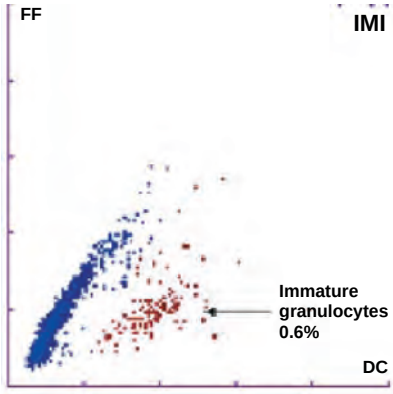

Fig. 27 *Enlarged IMI scattergram*

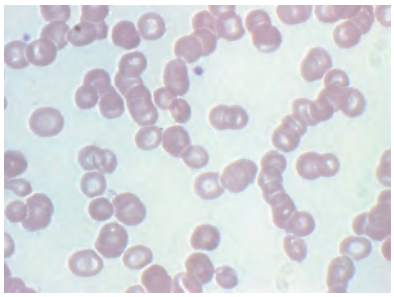

Fig. 28 *RBC rouleaux*

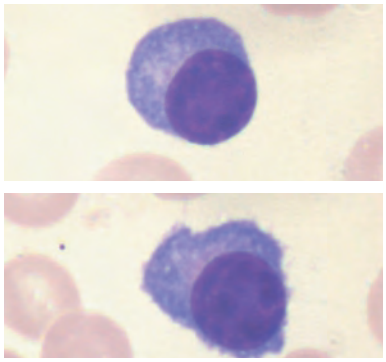

Fig. 29 *Plasma cells*

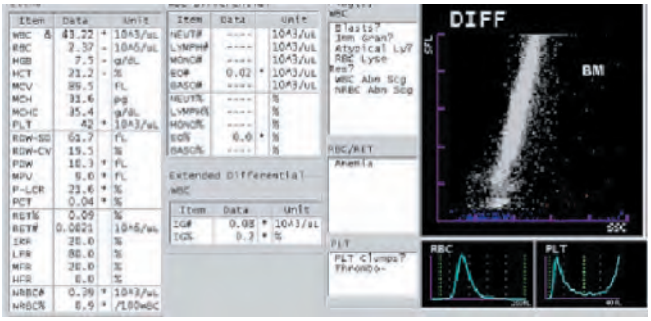

Fig. 30 *XE-2100 DIFF scattergram of plasma cell culture showing a monomorphic population similar to that of the patient's peripheral blood*

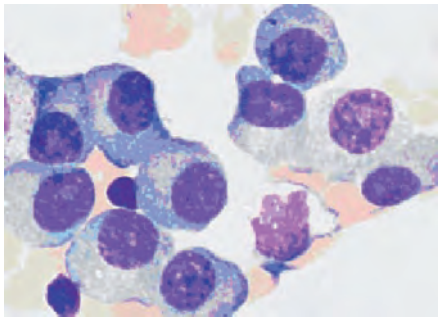

Fig. 31 *Bone marrow infiltration by mature plasma cells*

HAEMOGLOBIN H DISEASE

This section shows that the XE-2100 provides reliable NRBC and reticulocyte counts in α-thalassaemia intermedia (haemoglobin H disease). α-thalassaemia is the result of defective production of the alpha globin chain of haemoglobin. In haemoglobin H disease α chain synthesis is severely suppressed so that unstable tetramers of excess β globin chains (Hb H) are formed. Clinically haemoglobin H disease resembles β-thalassaemia intermedia.

The patient is a 6-year-old child with α-thalassaemia intermedia (deletion of three α globin genes (genotype --/-α)). The haemogram (***Fig. 32***) shows a haemoglobin concentration of 80g/L, an increased reticulocyte count at 329,000/μL (10.94 %), an increased immature reticulocyte fraction (IRF) at 41.4% and a high concentration of NRBC at 1,580/μL (13.8/100WBC) when measured on the XE-2100.

Punctate basophilia (***Fig. 33***) and Cabot rings (***Fig. 34***) were found in the peripheral blood smear. Hb H inclusions (***Fig. 35***) were found and the presence of Hb H was confirmed on electrophoresis.

In haemoglobin H disease patients, the abnormal haemoglobin has a high oxygen affinity and is unstable, precipitating to form intracellular inclusions (demonstrable on exposure to supravital staining (***Fig. 35***). This damages the red cells during their passage through the microcirculation. The result is a haemolytic anaemia, manifest, in the present patient, by an increased serum bilirubin, decreased haptoglobin level and an increased reticulocyte count with extremely elevated immature reticulocytes.

The DIFF scattergram is abnormal showing a cell cluster in the NRBC area (***Fig. 36***). The NRBC scattergram (***Fig. 37***) shows a high concentration of orthochromatic, polychromatic and even basophilic erythroblasts with excellent separation from the WBC. The RET scattergram illustrated in ***Fig. 38*** shows a high concentration of reticulocytes, IRF and the presence of microcytic erythrocytes.

The smear confirmed the pleomorphic nature of the NRBCs (orthochromatic erythroblast in ***Fig. 39*** and polychromatic erythroblast ***Fig. 40***).

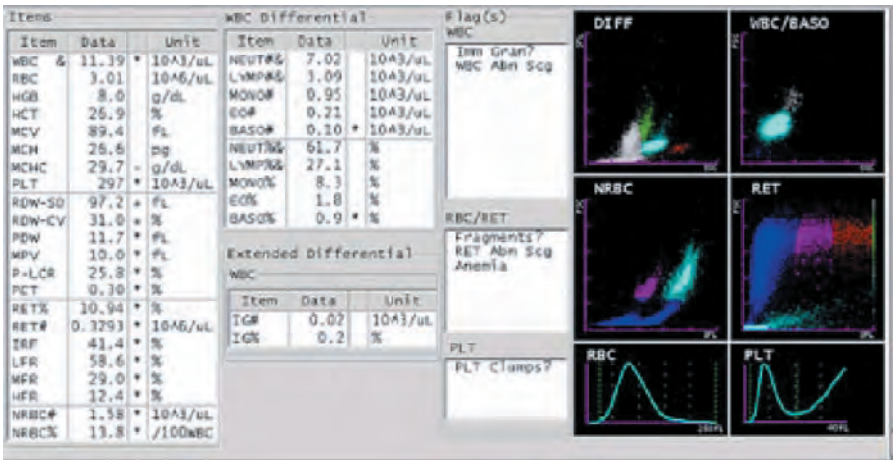

Fig. 32 *Presenting haemogram*

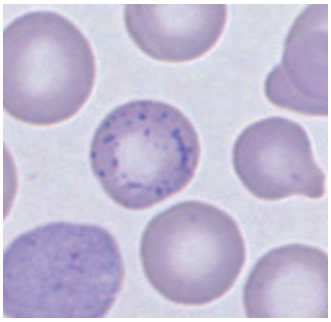

Fig. 33 *Punctate basophilia*

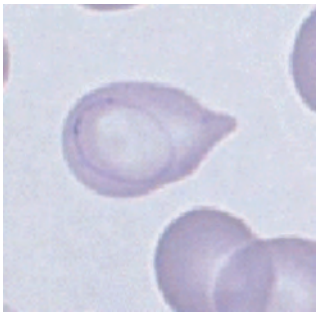

Fig. 34 *RBC containing Cabot ring*

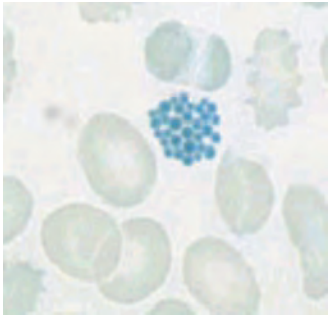

Fig. 35 *Hb H inclusions on supravital staining*

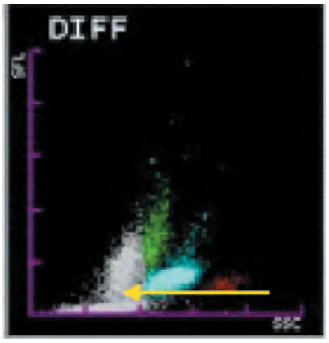

Fig. 36 *NRBC location indicated by "* ← *"*

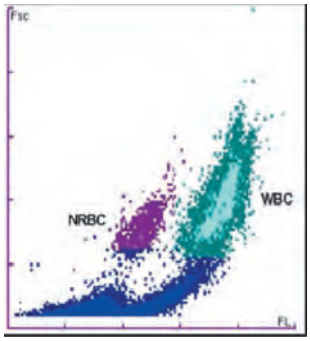

Fig. 37 *NRBC scattergram showing clear separation*

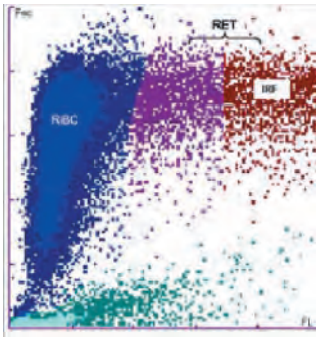

Fig. 38 *Reticulocyte scattergram*

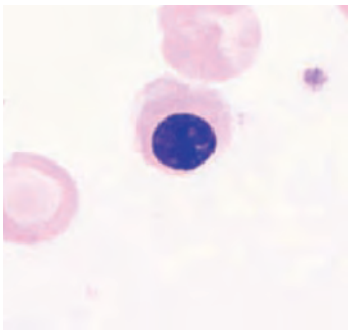

Fig. 39 *Orthochromatic NRBC*

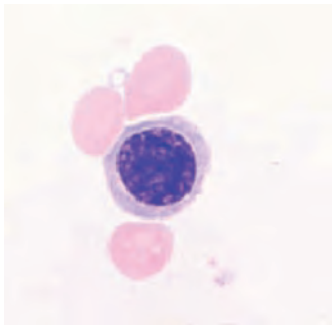

Fig. 40 *Polychromatic NRBC*

XE-2100 AND FALCIPARUM MALARIA

Typical XE-2100 DIFF scattergram appearances occur in heavy infestation with falciparum malaria, a phenomenon first reported by Briggs and Machin in 2001[7] (***Fig. 41***). This shows a tail of increased side fluorescence particles (purple dots) extending upwards from the monocyte cluster. A possible explanation of this high fluorescence activity could be the increased phagocytic activity of the monocytes ingesting malaria inclusions.

Reticulocyte parameters may also be of interest in untreated malaria. It has been noted that the absolute reticulocyte count may be increased but at the same time the immature reticulocyte fraction (IRF) is decreased. This is theoretically and practically impossible as these findings contradict each other in terms of reticulocyte physiology. It rather suggests, however, that the fluorescence activity of the cells counted represents inclusions which possess RNA/DNA, but which are not reticulocytes. These could be malarial parasites. The reticulocyte count is therefore falsely elevated due to this interference. A high absolute reticulocyte count and a low IRF may be a good indicator for malaria inclusions in the red blood cells however further confirmation of this observation is required.

This illustraitve patient is a 32-year-old male who presented with classic attacks of fever followed by identification of malaria parasites in a thick peripheral blood smear leading to a diagnosis of falciparum malaria (***Figs 42 and 43***). Lariam therapy was started immediately.

Figs 42 and 43 illustrate the morphological characteristics of falciparum malaria prior to Larium therapy. Note that the parasitised red cells are not enlarged, ring forms are delicate and there can be several in one cell; there may be two chromatin dots, but no developing forms are present and no gametocytes are found. The initial XE-2100 haemogram is illustrated in ***Fig. 44***.

There is thrombocytopenia but no anaemia and the leucocyte count is normal. The DIFF channel scattergram shows an abnormal population extending from the upper monocyte area (see 'a', ***Fig. 44***), indicating a higher fluorescence signal (RNA/DNA) than normal or even that produced by activated monocytes. The appearance is similar to that illustrated in ***Fig. 1***. The manual mono-

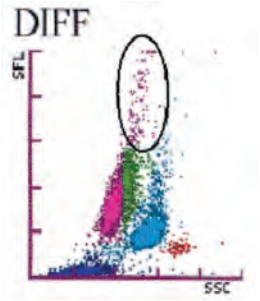

Fig. 41 *DIFF scattergram from a patient with 4.7% malaria parasitaemia (Briggs and Machin)*

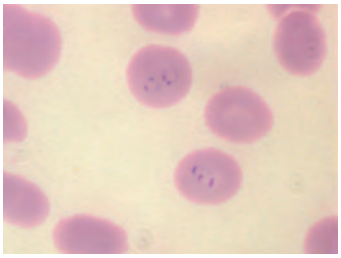

Fig. 42 *Malaria parasites in RBC*

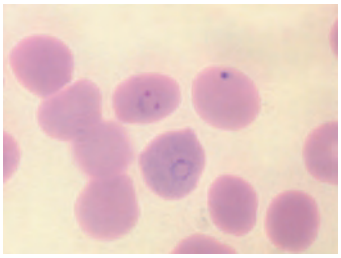

Fig. 43 *Malaria parasites in RBC*

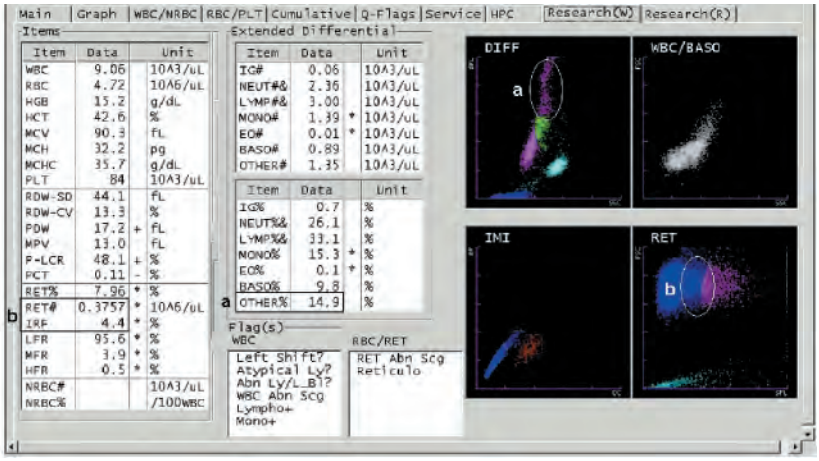

Fig. 44 *Initial XE-2100 haemogram*

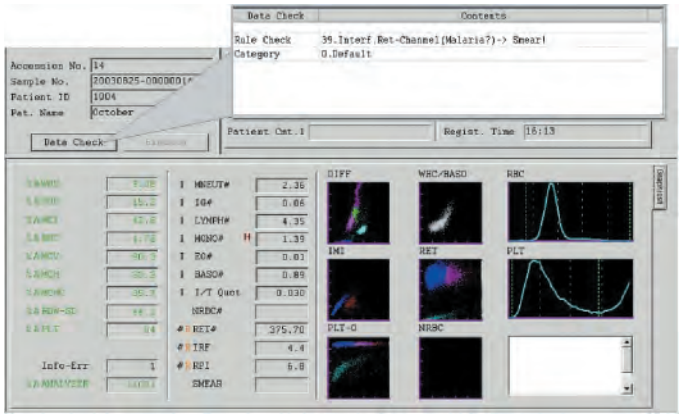

Fig. 45 *SIS result from this patient with an additional retest order (#R) for RET (Manual smear). See Rule 39*

Table 1 *Reticulocyte parameters after 12h of Larium therapy*

Registr. Time (h)	16:00	22:00	04:00
RET# (10^3 / μL)	375,7	244,3	116,2
IRF (%)	4,4	9,2	17,5
RPI (index)	6,8	4,8	1,4

cyte count is increased (26%) but this is not reflected by the instrument monocyte count (15.3%). However, if the 'OTHER' count (14.9%) is added to this, the resulting 30.2% is a closer approximation to the manual count. The reticulocyte count and RET-scattergram also show some interesting anomalies. The RET scattergram (see 'b', ***Fig. 44***) is abnormal between the RBCs (blue) and the reticulocytes (purple). The absolute reticulocyte count is increased, however the immature reticulocyte fraction (IRF) is decreased, the physiological contradiction described above and which may be a good indicator of malaria inclusions in the red blood cells. Although the elevated reticulocyte count is due to interference by malarial parasites, its serial measurement may indicate response to treatment. This hypothesis was tested in the present patient and appears to be valid as shown in ***Table 1***, the reticulocyte count (including RBCs with malaria inclusions) decreasing by a factor of 3 over a 12-hour period.

The reticulocyte abnormalities are included in the rule based Sysmex Information System (SIS) interface, shown in ***Fig. 45***. The rule guide, a combination of increased reticulocytes, decreased IRF and the flag "RET abn Scg" (see ***Fig. 44***), recommends and opens an additional order for a manual smear and reticulocyte count with the text "Rule 39: Interference RET Channel (Malaria?) - > Smear".

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