KAWASAKI MED. J. VOL. 11 : NO. 4, 191-213 (1985)

Computer-Assisted Laboratory Diagnosis and Its Clinical Usefulness

Susumu SHIBATA, Satoshi UEDA* and Nobuyoshi MATSUDA*

*Office of the Dean and *Department of Clinical Pathology, Kawasaki Medical School, Kurashiki 701-01, Japan*

Accepted for Publication on November 9, 1985

ABSTRACT. Clinical diagnosis based solely on the interpretation of laboratory tests without information regarding patient's morbid history and physical examination is now possible when properly selected tests are set in combination and carried out for the definite purposes of (1) appraisal of the patient's general condition, (2) assessment of hepatic, renal and pancreatic dysfunction, and (3) guessing the names of the patient's possible diseases. Interpretation of test results can now be carried out quickly and very efficiently by means of a computer. This is computer-assisted laboratory diagnosis or CALD. It was in 1970, 15 years ago, that the first primitive trial of such a system was carried out in Ube, Yamaguchi. Since then this system of CALD has evolved to the level that its use has become a part of daily routine in the Departments of Clinical Pathology of Kawasaki Medical School, Kurashiki, and Yamaguchi University School of Medicine, Ube. It was described to the members of the Korean Society of Clinical Pathologists in their general meeting held in Taegu in 1985.

Recently a team in the Department of Clinical Pathology of Tokai University Medical School in Isehara, Kanagawa Prefecture, was successful in developing another type of CALD. In the United States although trials of CALD were started in the 1970's, development has not been so rapid. At present, only a few laboratories are employing CALD. Aspects of CALD development in Japan and the USA will be described very briefly in the latter part of this article.

Key words : Computer — Computer interpretation — Computer-assisted laboratory diagnosis — Blood spectrum

Instruments and Progress of Medicine

It was in France at the beginning of the 19th century that marked progress was made in clinical medicine, namely with the invention of the stethoscope by Laennec (1816) (Fig. 1) and his development of indirect auscultation (1819).[1] Thereby the limitations in acquiring information on the pathology of a disease began to be removed. Before, the physician had depended upon unaided observations, but Laennec's achievements transformed medicine from little more than naive observation of the disease-status into a study based on more and more on sensitive examination aided by instruments. Since then, medicine has become equipped with technology which has made it possible to examine patients objectively and more precisely. In effect this represented the beginning of modern medicine.

Various medical devices such as the microscope, electrocardiograph, electroencephalograph, and the X-ray generator, are all characteristic of present-

柴田 進, 上田 智, 松田信義

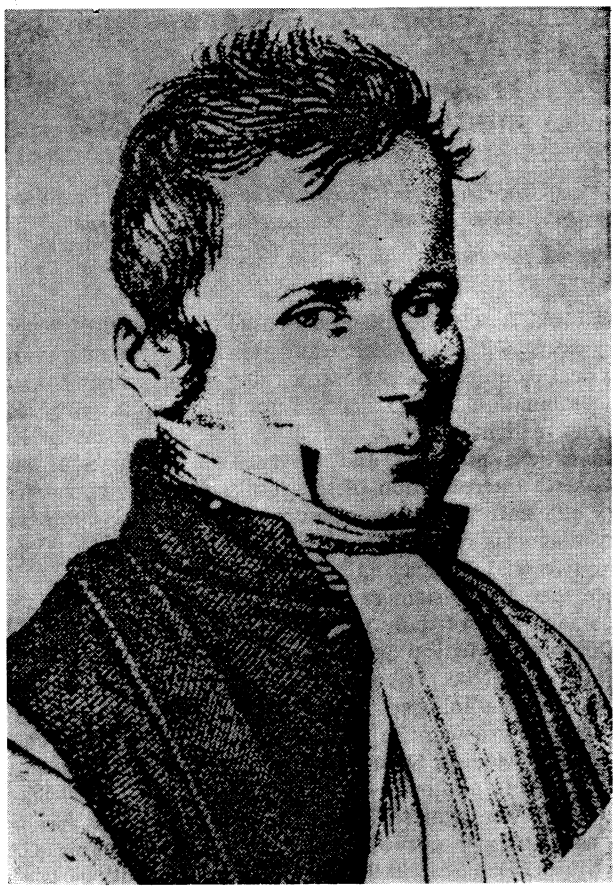


Fig. 1. R.T.H. Laennec (1781-1826). The inventor of stethoscope and indirect auscultation.

day medicine (Fig. 2). They also embody Laennec's idea that the fundamental purpose of medicine is to find signs of disease directly and accurately through the optimum use of available devices far more sensitive than one's natural senses alone. Keeping pace with the development of diagnostic devices, therapeutic progress has also been noteworthy. As a result, modern medicine has approached the level of a discipline worthy of the title "real medicine", by which pain is relieved, endangered lives are saved, and sick men recover their health.

The senior author of this article graduated from medical school about 45 years ago and was trained as an internist. In those days, to a certain degree, equipment (the microscope, X-ray machines, the electrocardiograph, etc.) was available for objective observation of patients, but therapeutic capacity lagged behind diagnostic ability. Internal medicine resembled biology in that doctors watched a disease ran its natural course. After being trained in internal medicine, he moved to laboratory medicine, where he stayed for 25 years. When he returned again to internal medicine 20 years ago, he was surprised at the changes that had taken place in the field : that is, that progress in examination techniques had made possible accurate diagnoses. The availability of many effective

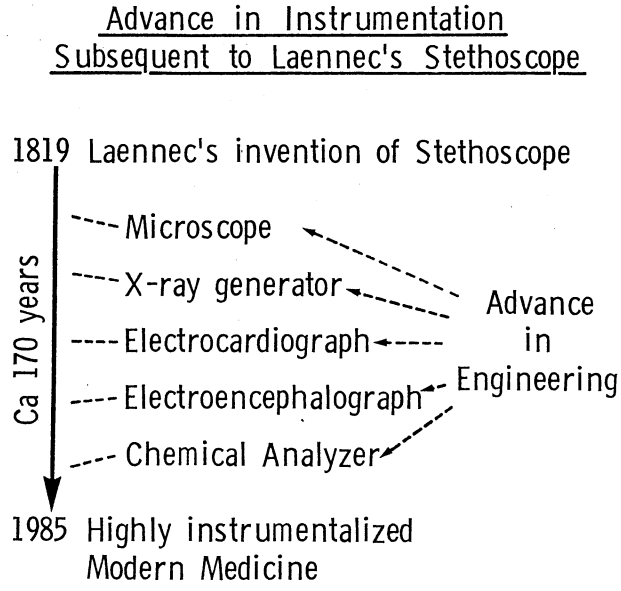


Fig. 2. Advance in instrumentation subsequent to Laennec's invention of stethoscope.

drugs had enabled physicians to say "We really feel that we are treating patients." He is therefore convinced that modern medicine has virtually succeeded in carrying out the primary purpose of medicine — to alleviate the patient's pain and to save endangered lives— by means of excellent examination techniques and effective drugs.

Three Steps in Examination of a Patient

In general, there are 3 steps taken in the examination of a patient : 1) The obtaining of proper knowledge of the patient's history and physical conditions through inspection, auscultation, and palpation ; that is, the classical physical examination ; 2) The performance of pertinent laboratory examinations such as urinalysis, stool examination, blood count, blood chemistry and electrocardiography ; that is, the laboratory examination ; and 3) The visualization of the inside of the patient's body directly and indirectly by endoscopy, roentgenography, echography, and radioisotopic detectors, in addition, occasionally, a portion of the body must also be resected to prepare a tissue specimen for microscopic examination. This third step can be summarized as image-visual diagnosis.

Diagnosis

By inspecting both the frontal and posterior aspects of a shield, one can determine what it is. Likewise, in modern medicine, by examining a patient from three different aspects ; by means of classical, laboratory, and image-visual examinations, a doctor can reach an accurate diagnosis. Unless a diagnosis is made from these 3 different perspectives, errors in recognition or misdiagnosis may occur. Laboratory and image-visual examinations are expensive, while the cost of the classical examination is comparatively lower. However, what would happen, if the examination of a patient concentrated on the classical method

alone and the other 2 methods were curtailed? Obviously, diagnosis would be back where it was in the days before Laennec. Although we would enjoy all the luxuries of the latter half of the 20th century we would be faced, when we became sick, with medical care of the low level that existed at the beginning of the 19th century.

Laboratory diagnosis, since it is called "diagnosis" should be carried out in the following manner : 1) The general condition of the patient should be noted as to whether it is slight, moderate or grave. 2) Functional disturbances of the vital organs such as the heart, lungs, liver and kidneys, which are most likely to be affected in any systemic illnesses should be elucidated. 3) Preferably, results should be interpreted for diagnostic purposes.

Diagnostic Guessing of Possible Disease Groups

Diagnosis is not essentially the same as simply guessing the name of a patient's disease from signs and symptoms of his illness without preliminary analytic consideration. First, a patient should be evaluated about general condition, and then he or she should be examined for the possible disease groups by employing rough classification, such as inflammatory diseases, collagen diseases, allergic diseases, neoplastic diseases, metabolic diseases and so forth. This process may be called diagnostic guessing of possible disease groups for patients. A final diagnosis will be established within the realm of these possible disease groups by the additional use of one or a small number of specific tests which should point to the presence of a particular disease when positive results are yielded. This is orthodox diagnostic procedure.

Tests which are useful for an assortment of the possible disease groups are

1. Cellulose acetate membrane electrophoresis of serum protein
and 2. Analysis of serum LDH isozyme patterns.

General Condition

Clinical chemists who work exclusively in laboratories have no direct contact with patients. Accordingly, all they can do is to appraise a patient's general condition through analysis of materials withdrawn from their body, such as body fluids.

A patient's nutritional state is the first criteria for the appraisal of his or her general condition since in everyday life it can easily be seen that healthy persons are well nourished, whereas malnutrition is inherent in patients, particularly in chronically ill subjects. In this sense, it may be said to a certain extent that nutritional state mirrors a patient's general condition.

Blood Chemical Ingredients Which Mirror Nutritional State

Blood is the tissue most easily obtained from the body of a patient. Through observation of the malnutrition and undernutrition prevalent among the people of nations defeated in the Second World War it has been recognized that blood hemoglobin concentration and serum protein content are reliable indicators for the appraisal of nutritional state.[2–7] In the early stage of declining nutrition the blood hemoglobin concentration usually starts to drop and slight anemia is commonly seen, while the serum protein concentration remains within normal range, but serum protein composition often begins to become abnormal,

that is, the albumin to globulin ratio falls below 1.0, the lower limit of its normal value. Decrease in albumin is compensated for by the increase in globulin, and thus the serum protein content, which is the sum of albumin and globulin, is maintained within the normal range until nutrition has been aggravated to the advanced stage of malnutrition associated with latent or overt edema. At this stage serum protein content falls below 6.5 g/dl, the lower limit of its normal range, and hypoproteinemia becomes evident, because the defect in serum protein content caused by diminished production of albumin is so marked that it can no longer be covered by the compensatory production of globulin.

Appraisal of General Condition — Hb-SP-A/G System

Since about 40 years ago, when clinical chemistry was still in the stage of resorting to the use of manual procedures, we have paid attention to the importance of evaluation of a patient's nutritional state by blood chemical examinations as a measure for extending the reliability of the classical physical examination for the assessment of a patient's general condition.

Based on the observations and studies previously mentioned we have been employing the blood hemoglobin concentration, the serum protein content and the serum albumin to globulin ratio as indicators for the appraisal of nutritional state and general condition. Recently we have been measuring serum cholinesterase activity for the same purpose.

The values of the estimations of these blood ingredients are graphically represented altogether in Figure 3. An easy understanding of the results can be obtained by glancing at the pattern of the line which connects the plotted points of estimations. Incidentally, fasting blood sugar level (BS) is plotted in this graph as an accessory not directly related to the assessment of general condition. The upper and lower limits of individual blood ingredients are shown by black nodules, and the scales of the parallel horizontal lines on which blood ingredients are plotted individually are adjusted so that the nodules form a rectangular circumscribed area of normal range.

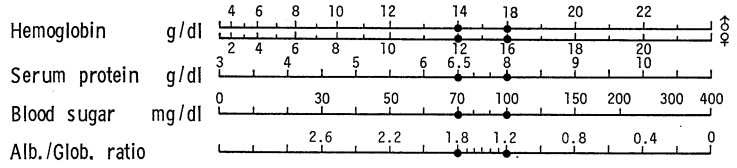


Fig. 3. Graphical representation of the estimations of blood chemical ingredients for the appraisal of patient's general condition—Hb-SP-A/G system.

Patterns of the Connecting Lines for Appraisal of General Condition — N, L, Z and F Patterns

The forms or patterns of the connecting lines for appraisal of general condition are classified roughly into the following 4 groups as shown in Figure 4.

Pattern N, in which all the plotted points of blood chemical ingredients lie within the rectangular area of the normal ranges. Normal healthy subjects and, occasionally, slightly ill patients display this pattern. N connotes "normal".

Pattern L, in which only one of the four plotted points is outside of the

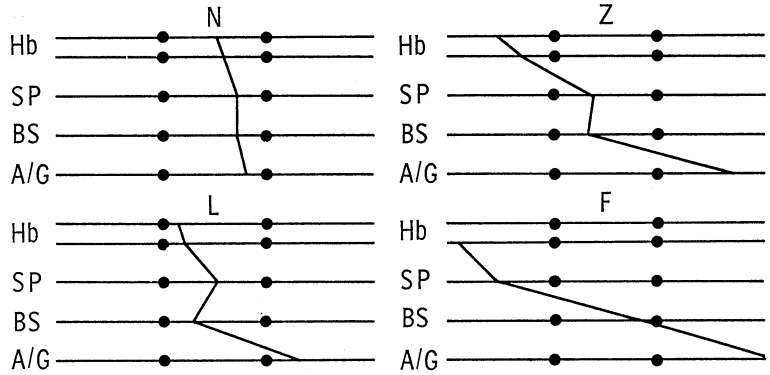


Fig. 4. Patterns of connecting lines for appraisal of general condition. N, L, Z and F patterns.

rectangular area of normal range. Usually, a decrease in hemoglobin concentration or a subnormal serum A/G ratio is noted. This pattern is commonly seen with slight depletion of general condition. The connecting line resembles the capital letter L.

Pattern Z, in which both the hemoglobin point and the A/G ratio point protrude from the rectangular area of normal range, while the serum protein plot remains within the normal area. The connecting line assumes the shape of Z which is deformed obliquely.

Pattern F, in which all the plotted points, except the BS point, are outside of the rectangular area of normal range. Markedly ill or almost dying patients with severe depletion of general condition display this pattern. The connecting line looks like it is falling side-ways. Therefore, we call this pattern F, taking F from the phrase "falling side-ways".

Comparison of the Patterns of Connecting Lines with the Clinically Assessed Depletion of General Condition

An example which demonstrates the usefulness of the connecting line patterns for the appraisal of general condition will be presented below.

Figure 5 shows the frequency distribution of the patterns N, L, Z and F of 87 seriously ill patients who died within *2* weeks after having had chemical examination of their blood samples. It is seen that pattern F and Z are about 40 and 30 in number, respectively, while those of patients displaying patterns N and L are less than ten. Patterns F and Z, which indicate severe and moderate depletion, respectively, overwhelm patterns N and L, which indicate no depletion or slight depletion, respectively.

Nowadays, the grouping, of many patients into patterns N, L, Z and F can be carried out rapidly and easily by use of a computer.

Appraisal of General Condition — Alb-SP-ChE System

When samples of anticoagulated blood are not obtainable from patients, the appraisal of general condition by chemical examination of the Hb-SP-A/G system, of course, becomes impossible. In such a case, the Alb-SP-ChE system, in which chemical analysis of blood serum exclusively is carried out, is available as a substitute. In this system the concentrations of total protein (SP) and

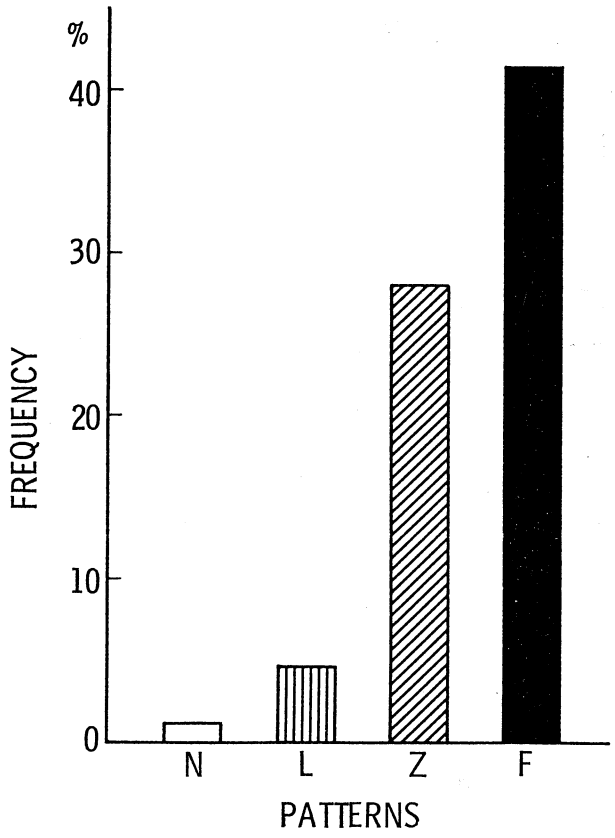


Fig. 5. Frequency distribution of the patterns N, L, Z and F of 87 seriously ill patients who died within 2 weeks after having had chemical examination of their blood samples.

serum albumin (Alb) and the activity of serum cholinesterase (ChE)[8] are estimated, and the estimated values are put into the equation shown in Table 1, and the discrimination value (DV) for the appraisal of general condition is calculated by computer.

Based on the DV, general condition is assessed as normal, slight, moderate or severe depletion.[9]

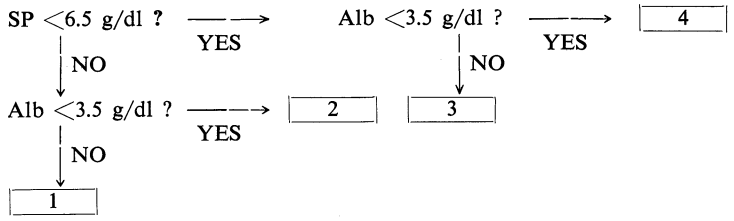
Figure 6, which compares the depletion of the general condition of outpatients with that of inpatients seriously ill and almost dying. This figure shows that the number of patients with no or slight depletion is overwhelmingly large in the outpatient clinic. This is in marked contrast to the distinct preponderance of severe depletion among critically ill inpatients.

Hepatic, Renal and Pancreatic Tests[9]

Impaired function of major metabolic organs governs the general condition and prognosis.

The heart, the lungs, the liver, the pancreas, the kidneys and the central nervous system are the important organs regulating the vital signs of normal subjects. These organs endure bodily hardship when persons are sick, and,

TABLE 1. Appraisal of general condition by Alb-SP-ChE system and the equation for calculating discrimination value (DV).



1	SP≧6.5 g/dl and Alb≧3.5g/dl ·····no depletion
2	SP≧6.5g/dl, but Alb<3.5g/dl
	2-1 DV≦5 ·····slight depletion
	2-2 DV>5 ·····moderate depletion
3−1	6.1g/dl<SP<6.5g/dl, but Alb≧3.5g/dl
	3-1 DV<4 ·····slight depletion
	3-2 4≦DV<5.5 ·····slight to moderate depletion
	3-3 DV<5.5 ·····moderate depletion
3−2	SP≦6.1g/dl, but Alb≧3.5g/dl ·····moderate depletion
4	SP<6.5g/dl and Alb <3.5g/dl
	Neither 4-1, nor 4-2 ·····moderate to severe depletion
	4-2 SP≦5.5g/dl, Alb≦2.9g/dl and DV>5.5·····severe depletion

SP : serum protein (g/dl) Alb : Albumin (g/dl) ChE : Cholinesterase (IU/dl)
Discrimination equation : $0.833\times(0.253\times SP-4.249\times Alb-1.946\times ChE(\Delta pH)$
$+18.274)ChE(\Delta pH)$
$=0.55\times(ChE(IU/dl)-240)/250+0.65=DV$

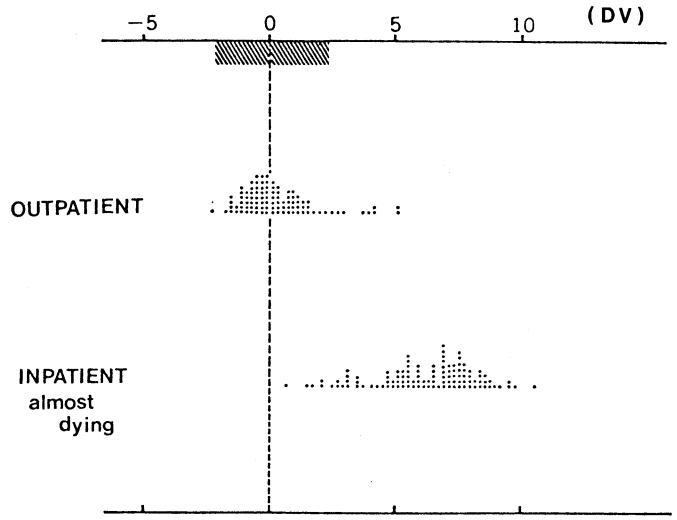


Fig. 6. Appraisal of general condition by Alb-SP-ChE system. Outpatient in comparison with inpatient (almost dying).

therefore, their function is disturbed more or less seriously in most patients. To our regret, blood chemical analysis can not always reveal all the aspects of dysfunctions of these organs. At present only the liver, the pancreas and the kidneys may be mentioned as the organs whose dysfunction is detectable

by blood chemical analyses. These analyses are employed in our computer-assisted laboratory diagnosis as hepatic tests, pancreatic tests and renal tests and are listed in Table 2.

TABLE 2. Hepatic, renal and pancreatic tests.

(1)	Hepatic tests
	For detection and appraisal of jaundice
	II : serum icteric index (4~6)
	Bil (T) : total serum bilirubin (0.2~1.0 mg/dl)
	For detection and appraisal of biliary obstruction
	Bil (D) : direct serum bilirubin (40~60% of bil(T))
	AlP : serum alkaline phosphatase (25~80 IU/l)
	Cho : serum cholesterol (130~220 mg/dl)
	γ-GTP : serum γ-glutamyl transpeptidase (0~30 IU/l)
	For detection and appraisal of hepatic cell damage
	LDH : serum lactic acid dehydrogenase (49~92 IU/l)
	Alb : serum albumin (3.5~5.0 g/dl)
	Glb : serum globulin (2.5~4.0 g/dl)
	ChE : serum cholinesterase (240~490 IU/dl)
	GPT : serum glutamic pyruvic transaminase (0~25 IU/l)
	GOT : serum glutamic oxalacetic transaminase (0~20 IU/l)
(2)	Renal tests
	Crn : serum creatinine (0.8~1.5 mg/dl)
	BUN : serum urea (9~20 mg/dl)
	UrA : serum uric acid (2.5~8.0 mg/dl)
(3)	Pancreatic test
	Amy : serum amylase (100~460 IU/l)

Computer-Assisted Laboratory Diagnosis

Blood chemical tests are classified according to their diagnostic purposes : (1) Those for the appraisal of general condition, (2) those for the detection or appraisal of hepatic, pancreatic and renal functions, and (3) those for examining the range of the possible disease groups. The tests of these 3 groups are carried out simultaneously with the same single blood sample, and the test results are subjected to synthetic interpretation and enumeration of possible diseases by use of a computer.

Blood Spectrum

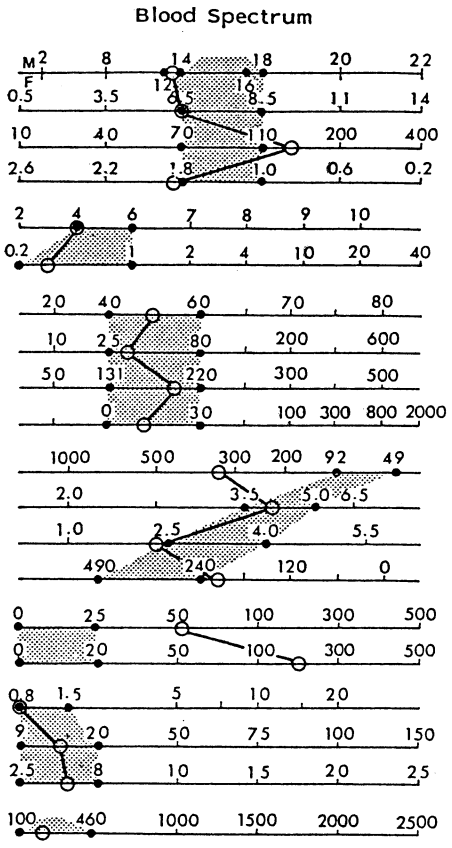
We refer to test group (1), including the Hb-SP-BS-A/G system or the SP-BS-ChE system in conjunction with test group (2), which is composed of the hepatic test system, the renal test system, and the pancreatic test system as the "blood spectrum",[10-12] because these tests enable us to make a blood chemical diagnosis without the aid of information regarding the morbid history or the clinical signs and symptoms of a patient. A computer can deal with the synthetic interpretation of many blood spectrums within a very short time in a completely rule-bound standard manner.[13] It is mandatory, however, that the software for such computer diagnosis be made by clinical chemists. Only clinical chemists are capable of compiling a software diagram for diagnostic purposes. They must prepare diagnostic codes themselves on the basis of their laboratory experience and by collating accumulated laboratory test results regarding clinical symptoms and signs described in medical records.

At present we have about 180 diagnostic codes available. Our personal computers can make a computer-assisted diagnosis based on the blood spectrum

of one case in 15 seconds on the average. Estimation values of all tests together with graphical representations and a list of possible clinical diagnoses, 10 at maximum, are printed out successively, in the order of their probability.[14]

Now two examples of computer-assisted diagnosis and diagnostic codes, that is Dx codes, are presented below.

Case #1 A 48-year-old man employed by the governmental railway company. The patient's blood chemistry is depicted in Figure 7. Hemoglobin was



Item	Estimations	
Hb	12.6	g/dl
SP	6.5	g/dl
BS	148	mg/dl
A/G	1.82	
II	4	
Bil(T)	0.4	mg/dl
Bil(D)	50.0	%
AlP	29	I.U./l
Cho	192	mg/dl
γGTP	13	I.U./l
LDH	340	I.U./l
Alb	4.2	g/dl
Glb	2.3	g/dl
ChE	229	I.U./dl
GPT	51	I.U./l
GOT	190	I.U./l
Crn	0.8	mg/dl
BUN	13	mg/dl
UrA	5.7	mg/dl
Amy	153	I.U./l

Fig. 7. The blood spectrum of case #1.

lowered, serum protein was normal, and blood sugar was elevated, connoting the presence of hyperglycemia. The serum A/G ratio was within normal range. The connecting line shows that only hemoglobin is outside of the normal rectangular area, if blood sugar may be discounted, since it is not directly concerned with the change in general condition. The impairment of general condition is appraised as slight depletion, because the connecting line is thought to be a subtype of the L pattern. The patient thus appears to be a man slightly ill with hyperglycemia. What is the cause of this hyperglycemia?

The serum icteric index and serum bilirubin are graphically represented in the same figure. Apparently there is no jaundice, because both the icteric index

and serum bilirubin are within the normal range, both being rather close to their lower limits.

The graph of hepatic tests indicates that there is no biliary obstruction. Indicators of biliary obstruction, such as direct serum bilirubin, alkaline phosphatase, serum cholesterol and γ-glutamic transpeptidase, are all within the frame area of normal range.

The graphical representation of the tests for parenchymatous hepatic cell damage, however, shows abnormalities. Serum LDH activity is raised to a considerably high level, serum globulin concentration is slightly subnormal, and serum cholinesterase activity is also questionably decreased.

Elevation of LDH activity and reduction of cholinesterase activity are consistent with hepatic parenchymatous damage, but lowered serum globulin, namely absence of hyperglobulinemia, seems to be somewhat inconsistent with ordinary hepatic parenchymatous damage, casting some doubt on its plausibility. On the other hand, there is a distinct rise in the activities of serum transaminases, that is, GPT and GOT. At a cursory glance, this finding may point to hepatic parenchymatous damage. Here, our attention should be attracted to the fact that GOT is almost 4 times higher in activity than GPT. If an increase in transaminase activity is caused by hepatitis, GPT is higher than GOT. If such an increase is related to liver cirrhosis, GOT may be higher than GPT, but in this case we can see that serum globulin has not increased. What is the cause then of this elevated GOT which is disproportionately higher than GPT? It is thought that there may be damage to the heart muscles, which contain larger amounts of GOT than GPT. The increase in LDH, which has been mentioned, also supports the possibility of muscle damage. It may be possible that the patient has a myocardial infarction in conjunction with anicteric hepatic damage. If he has a myocardial infarction, the chest pain may be causing outbursts of adrenaline from the adrenal medulla which result in hyperglycemia due to increased glycolysis by adrenaline.

The graph of renal tests shows that the patient has no advanced renal disorders. The graph illustrates normal plotted points of creatinine, BUN and uric acid. Serum amylase is also within the normal range, connoting the absence of a gross pancreatic lesion.

The Guess of Possible Disease Groups

Because there was an increase in serum LDH, an isozyme study of this enzyme was carried out simultaneously. The result is depicted in Figure 8. Total LDH activity rose incessantly with the lapse of time after admission. It reached its acme 14 hours after onset of the disease, and descended slowly until 10 days later when it returned to normal range. As will be seen in this figure, the isozyme LDH_1, which originates in the heart muscle was the most predominant, while LDH_5, which pertains to the liver, was the least in amount throughout the course of the patient's illness. This LDH isozyme pattern is contradictory to neoplastic disease. A neoplasm, therefore may be excluded.

It is germane to diagnose the patient as follows from the analysis of his blood spectrum.

1. The patient was a 48-year-old male who displayed the sudden onset of a myocardial infarction.

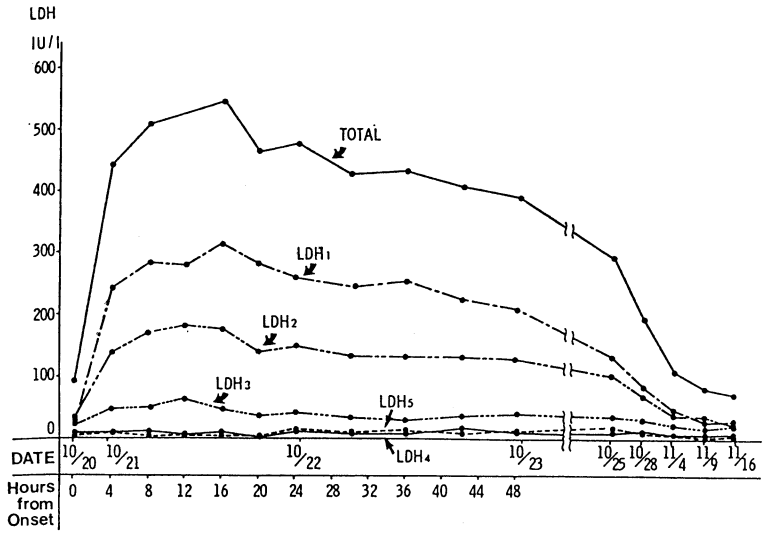


Fig. 8. Serum LDH isozyme study of case #1.

2. His general condition was not so seriously impaired, although he had a slight anicteric hepatic disturbance.
3. Renal and pancreatic functions were within the normal range.

Computer-Assisted Laboratory Diagnosis

Computer-assisted laboratory diagnosis is shown in Figure 9.

This shows the graphical representation and the comments of the blood spectrum printed out by our computer.

The computer says

1. There is no depletion
2. Hyperglycemia
3. Myocardial infarction?
4. Anemia, mild (follow up)
5. Multiorgan injuries.

This diagnosis was derived from the diagnostic codes installed in the software of our computer, which are shown in Table 3.

Case Record of Case #1 — Morbid History and Physical Examination

The patient (male, aged 48) was an employee of the Government Railway Company who had a desk job. It was about 3 years ago that his family physician informed him that he had hypertension. He received treatment for the disease, but stopped taking prescribed medicine about six months ago. At about 11 o'clock on the night of November 20th he suddenly experienced the onset of burning pain in the retrosternal area while sleeping with his wife in bed. He became dyspneic and agonized, squatting down on the bed. He was soon transported to the Emergency Department of Kawasaki Medical School Hospital. He did not drink regularly, but smoked about 20 cigarettes daily.

At the outpatient clinic his vital signs were : pulse rate 74, respiration rate

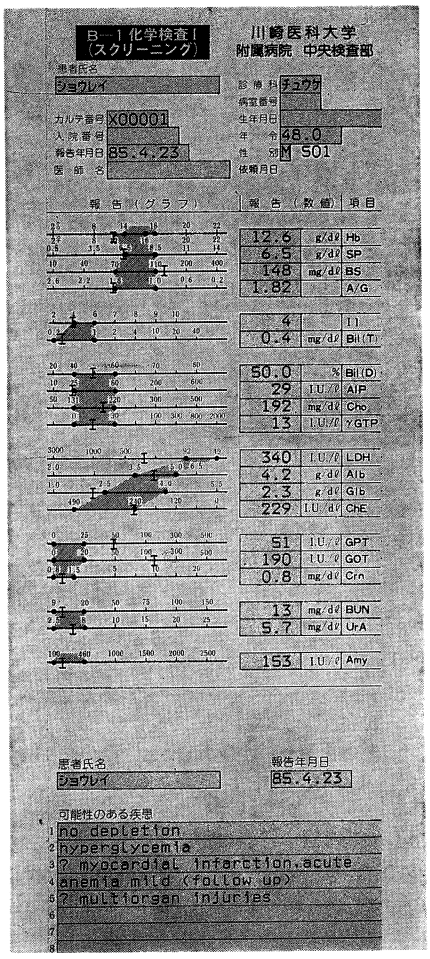


Fig. 9. Report sheet of computer-assisted laboratory diagnosis of case #1.

17 and blood pressure 120/70 torr. His chest was negative to auscultation and percussion. The abdomen was normal. Normal tendon reflexes were elicited. The sublingual application of a nitroglycerine tablet was not effective for the alleviation of retrosternal pain. A plain X-ray film of the chest revealed the cardiothoracic ratio to be enlarged to 56%.

The patient's electrocardiogram was of the pattern characteristic of acute myocardial infarction. The ST segment was elevated distinctly in V_2 and V_3 leads.

The patient's serum CPK (creatine phosphokinase) was within the normal range at the time when he was transported to the Emergency Department, but it soon commenced to rise steeply and attained its acme of 2000 IU/l 8 to 9 hours after the onset of chest pain and then returned to its normal range on the fourth admission day. The CPK isozyme was 78% MM and 22% MB at the peak of total CPK elevation.

The patient's condition took a favorable course following intravenous

TABLE 3. Diagnostic codes (Blood chemistry).

Dx code 67	·····	*hepatitis (anicteric)*
Patient		Range
LDH 340 IU/l	·····	201 ~ 500
ChE 229 IU/dl	·····	150 ~ 236
GPT 51 IU/l	·····	26 ~ 100
GOT 190 IU/l	·····	126 ~ 300
Dx code 136	·····	*hyperglycemia*
Patient		Range
BS 148 mg/dl	·····	121 ~ 160
Dx code 111	·····	*myocardial infarction, acute ?*
Patient		Range
LDH 340 IU/l	·····	201 ~ 500
GPT 51 IU/l	·····	26 ~ 100
GOT 190 IU/l	·····	126 ~ 300
GOT/GPT 3.7	·····	2 ~ 999.9
Dx code 86	·····	*anemia, mild (follow up)*
Patient		Range
Hb 12.6 g/dl	·····	10 ~ 12.9
ChE 229 IU/l	·····	150 ~ 236
Dx code 35	·····	*multiorgan injuries*
Patient		Range
LDH 340 IU/l	·····	201 ~ 500
GOT 190 IU/l	·····	126 ~ 300
GOT/GPT 3.7	·····	2 ~ 999.9

injection of urokinase, and he was discharged from the hospital 3 weeks after admission.

Case #2 A 77-year-old female

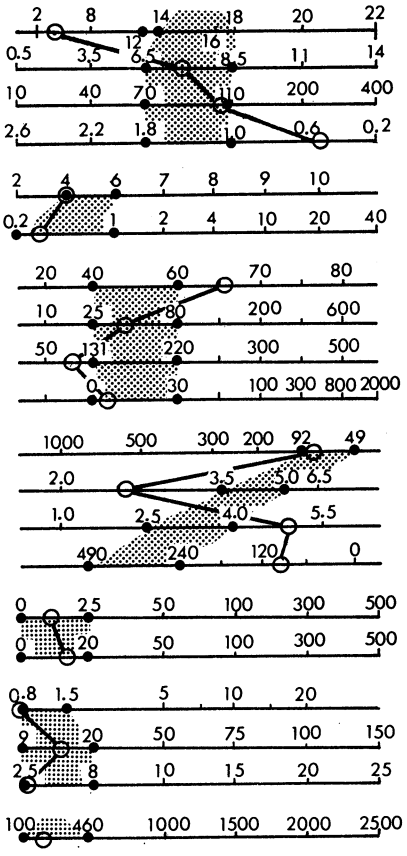
This is a female patient, aged 77. Her blood spectrum is shown in Figure 10. Blood hemoglobin was at about 1/3 the level of that of a normal subject. Serum protein was, however, within normal range. There might be questionable hyperglycemia. The serum A/G ratio was distinctly lowered.

The connecting line is Z-shaped, connoting moderate or severe depletion. The anemia, which has been pointed out, is severe. Presumably, the anemia will be the most important problem.

Figure 10 shows that the patient has no jaundice. The icteric index and the total serum bilirubin are around the lower limit of the normal range, being consistent with severe depletion, the presence of which has been presumed from the graph of Hb-SP-BS-A/G system.

As to the indicators for biliary obstruction, two of them, that is, the percentage of direct bilirubin and serum cholesterol, are out of the normal range. It is of special note that her serum cholesterol concentration is extremely low. This suggests the presence of either a severe hepatic dysfunction impairing the synthesis and absorption of cholesterol, malnutrition, or hyperthyroidism. Attention should be paid to the fact that the indicators specific for the sign of biliary obstruction, namely serum alkaline phosphatase and γ-GTP, are within normal range. In addition, as was realized earlier, her serum bilirubin was normal. Accordingly, it is thought that there is no biliary obstruction.

As seen from the graph of LDH-Alb-Glb-ChE system, three of the four



Item	Estimations	
Hb	5.1	g/dl
SP	7.3	g/dl
BS	102	mg/dl
A/G	0.48	
I1	4	
Bil(T)	0.3	mg/dl
Bil(D)	66.0	%
AlP	42	I.U./l
Cho	95	mg/dl
γGTP	4	I.U./l
LDH	79	I.U./l
Alb	2.4	g/dl
Glb	4.9	g/dl
ChE	98	I.U./dl
GPT	11	I.U./l
GOT	14	I.U./l
Crn	0.6	mg/dl
BUN	15	mg/dl
UrA	2.6	mg/dl
Amy	178	I.U./l

Fig. 10. Blood spectrum of case #2.

indicators of hepatic parenchymatous damage were outside the normal range. Only her serum LDH is normal. There was a marked decrease in serum albumin. On the other hand, globulin distinctly increased. This hyperglobulinemia connotes inflammatory disease, and hypoalbuminemia is indicative of malnutrion or neoplastic disease. Scrutiny of the connecting line on the whole suggests that the patient has had an anicteric hepatic dysfunction. Hepatic cellular damage is not conceivable, however, since transaminases, that is GPT and GOT, are within normal range.

Renal and Pancreatic Tests of Case #2

Figure 10 indicates that there is neither a significant renal disturbance nor acute pancreatic damage, because serum creatinine, BUN, serum uric acid and serum amylase are all within normal range.

Possible Disease Groups of Case #2

To guess the possible disease group it is recommended that cellulose acetate membrane electrophoresis be done or that the serum LDH isozymes be examined. It is fortunate for us that electrophoresis of the serum protein of this

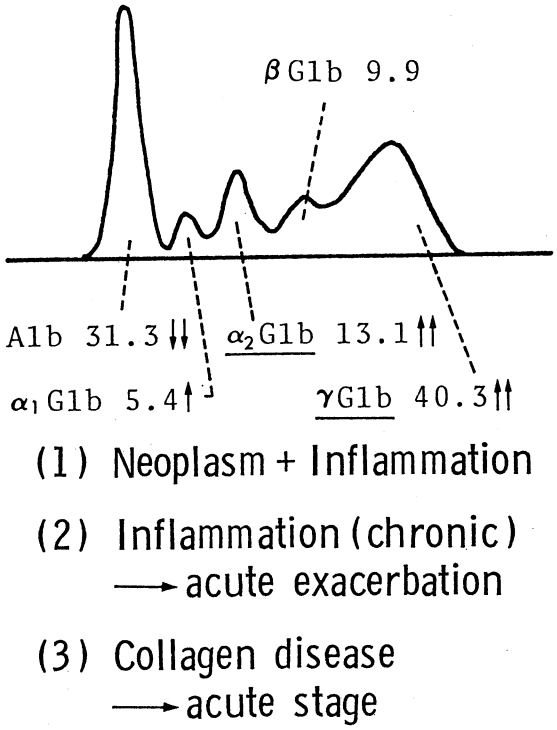


Fig. 11. Cellulose acetate membrane electrophoresis of serum protein (Case #2).

patient was done. The results of the test are presented in Figure 11.

It is apparent from the figure that serum albumin decreased remarkably. On the contrary α_1, α_2 and γ globulins have increased. The increases in α_2 globulin and in γ globulin are particularly distinct. This finding is suggestive of the possibility of one of the following pathological conditions, namely,

(1) neoplastic disease accompanied by inflammation,
(2) acute exacerbation of chronic inflammation, or
(3) the acute stage or exacerbation of collagen diseases.

As easily seen from Figure 10, this lady has profound anemia. If we take this anemia into consideration, we might be lead to the assumption that she has a neoplastic disease which causes the profound anemia, together with an inflammatory complication. If so, it will be impossible to make a final diagnosis on the basis of her blood spectrum alone.

The computer-assisted blood chemical diagnosis provided us with the following list of possible pathological considerations as listed below

1. Moderate depletion
2. Inflammatory disease
3. Malignacy?
4. Anemia, moderate (detailed hematological examination)
5. Gammopathy? (detailed serum protein examination)
6. Hemodilution

Now it has become evident that a hematological examination was urgently

needed for the diagnosis of this patient. Recently routine hematological examinations have been remarkably auto-instrumentalized as well as computerized owing to the rapid development of engineering. The Wright-stained peripheral blood smear of the patient was scanned in an automatic morphological cell analyzer, like Sysmex Cell Analyzer, and her blood was subjected to it. This gave us not only RBC, WBC and platelet counts, but also the indexes of MCV (90.0 fl), MCH (35.0 pg) and MCHC (37.5%) as shown in Table 4a,b.

TABLE 4a. Hematological report.

149*	RBC	$\times 10^4/\mu l$	(420–600)
5.1*	Hb	g/dl	(12.0–17.5)
13.6*	Ht	%	(34–52)
90.0	MCV	fl	(82–101)
35.0	MCH	pg	(27–34)
37.5*	MCHC	%	(32–36)
1.7*	Reticulocyte	%	(0.5–1.5)
	OCCA Diff. basophilic		
	PLATELET		
15.3	Direct count	$\times 10^4/\mu l$	(15–35)
1000*	WBC	$/\mu l$	(4,000–10,000)
WBC DIFFERENTIAL COUNT (%)			
8.0*	Blast (or pathol. cell)		
0.0	Progranulo		
0.0	N. Myelocyte		
0.0	N. Metamyelocyte		
4.0	N. Band		(2–10)
8.0*	N. Segmented		(50–70)
0.0*	Eosinophil		(1–5)
0.0	Basophil		(0–1)
0.0*	Monocyte		(1–6)
80.0	Lymphocyte		(20–40)
0.0	atypical Lympho		
2.0*	Rubricyte		/100 WBC
0.0	Megalocyte		/100 WBC
0.0	Megakaryocyte		/100 WBC
0.0	Auer rod		/100 Blastoid
	Platelet count Fonio	$\times 10^4/\mu l$	
	Platelet Forming clumps		

MORPHOLOGY		
ANISOCYTOSIS		SLIGHT
SIZE	normo	* %
	micro	%
	macro	%
Color	ortho	* %
	hypo	%
	poly	%
POIKILOCYTOSIS		SLIGHT
1	pointed cell	
2	Basophilic stippling	
3	Howell-Jolly body	
4	Rouleaux formation	
5	Target cell	
6	Ovalocyte	
7	Bizarre cell	
8	Red cell fragment	
9	Microspherocyte	
10	Döhle body	
11	Toxic granules	
12	Vacuoles	
13	Hyperseg. N.	
14	Crenated cell	
15	Burr cell	
16	Leptocyte	
17	Elliptocyte	

TABLE 4b. Computer-Assisted Laboratory Diagnosis (Hematological).

Possible Diagnoses, Abnormalities and Notes

1. *Leukemia*
   blastoid cell–8, Auer–0, Hiatus (+)
   low WBC–1000, plt–15.3
2. *Agtanulocytosis*
   neutroph.–12.0
3. *Plt-normal*
   plt–15.3
4. *Pure red cell aplasia*
   anemia-severe, low Hb–5.1
   normochromia
   low retic. index–0.5

NOTE : Check BM smear.
Drug-induced ? High risk of infection.
Check BM. Thymoma ? Myasthenia ??
Refer to hematologist

The RBC ($149\times10^4/\mu l$), Hb (5.1 g/dl) and Ht (13.6 %) were all at the critical value level. Both WBC and platelet counts were low.

Therefore, the patient had pancytopenia.

Peripheral Blood Smear (Wright-stained) and Differential Cell Count of Case #2

What, however, is the essential cause of this pancytopenia? Is it aplastic anemia? No, this it is not. Scrutiny of individual cell, however, reveals a significant number of agglomerated erythrocytes and rare leukocytes. The rouleaux formation of erythrocytes is consistent with hyperglobulinemia. Immature leukocytes were encountered, though they were rare.

The differential count of leukocytes disclosed that blastoid cells occupied 8.0%, progranulocytes 0%, N. segmented 8.0%, lymphocytes 80%, and monocytes 0%.

This finding is consistent with acute aleukemic leukemia of presumably granulocytic type with distinct hiatus leukemicus.

The computer-assisted-hematological diagnosis[15,16] is as shown in Tables 4a,b and 5. (Table 5 presents diagnostic codes[15]).

TABLE 5. Hematological diagnostic codes (peripheral blood).

Dx code 1 ·····*Leukemia*				
Check BM smear				
blastoid cell (−)	*blastoid cell* (+)	*blastoid cell-X* (>0)		
Auer rod (−)	Auer rod(+)	Auer rod-		
low WBC-	? low WBC-	WBC-	? high WBC-	high WBC-
no hiatus	hiatus (+)			
low plt-	*plt-*	high plt-		
Dx code 80 ·····*Agranulocytosis*				
Drug-induced ?	High risk of infection			
neutroph. (−)	neutroph. (+)	*neutroph.-X*(<500)		
Dx code 131 ·····*Plt-normal*				
low plt-	*Plt-X (14-45)*	high plt-		
Dx code 83 ·····*Pure red cell aplasia*				
Check BM.	Thymoma ?	Myasthenia ? anemia		
low Hb-X (<7)	Hb- *normochromia*	high Hb- hypochromia	anisochromia	high retic. index
retic. index-0	retic. index (+)	*low retic. index-* (≦0.5)	retic. index-	

That is

1. Acute leukemia
2. Agranulocytosis
3. Thrombocytopenia absent
4. Pure red cell aplasia

with additional remarks or recommendations

1. Bone marrow smear examinations
2. Rule out drug-induced disease
3. High risk of infection
4. Estimation of serum folate and VB_{12}
5. Malignancy other than leukemia.

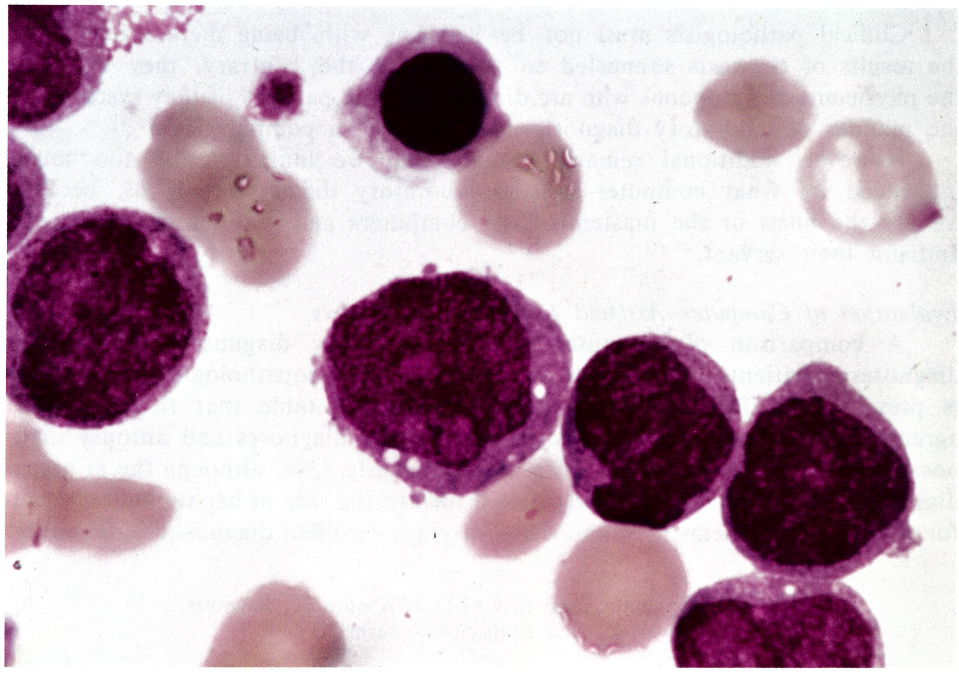


Fig. 12. Bone marrow aspirate smear of the patient (Case #2).

The findings of the bone marrow smear are shown in Figure 12. Numerous immature granulocytic cells are seen. They were positive for peroxydase stain. This connotes a diagnosis of acute leukemia, probably of M_2 type according to the FAB classification.[17]

Case Record of Case #2

This female patient, aged 77, had a pyrexia of 39°C which lasted for a few days in January, 1982. She thought she had a common cold. However, when she visited her physician, she was told that she had pancytopenia and was introduced to the Division of Hematology of Kawasaki Medical School Hospital.

On admission she was distinctly pale in complexion, but neither petechiae nor purpurae were seen on mucocutaneous tissue. There was no lymphadenopathy. The chest was clear to percussion and auscultation, but her chest X-ray film revealed that she had pneumonia. The abdomen was negative without splenomegaly. The antinuclear antibody test was negative, the RA test positive and the cold agglutinin titer elevated.

DOAP therapy[18] and DCMP therapy[18] failed to produce remission, and she died because of spesis (Pseudomonas cepacia, Streptococcus faecalis, Candida albicans) on April 12.

These 2 examples which have been presented are thought to have illustrated that, even though clinical pathologists do not see patient directly, they can guess the names of their diseases by use of computer-assisted laboratory diagnosis. The reports issued from the laboratory would surely have been helpful to the physicians who were in charge of the care and cure of the patients.

Clinical pathologists must not be satisfied with being mere reporters of the results of the tests submitted to them. On the contrary, they can join the physicians and surgeons who are directly treating patients, if they systematize the manner of laboratory diagnosis by the use of a computer.

However, additional remark is made that we must not be too much influenced by what computer-assisted laboratory diagnosis tells us, because we are the hosts or the masters of the computers and automatic instruments, and not their servant.

Evaluation of Computer-Assisted Laboratory Diagnosis

A comparison of computer-assisted laboratory diagnoses and autopsy diagnoses of patients we discussed in our reversed clinicopathological conferences is presented in Table 6. It is apparent from the table that there is good agreement between computer-assisted laboratory diagnoses and autopsy diagnoses. The agreement obtained was approximately 93%, although the principal diseases of the patients are fairly biased toward the side of hepatorenal diseases for which blood chemical examination displays excellent diagnostic potentiality.

TABLE 6. Comparison of CALD with autopsy diagnosis about various cases subjected to reversed CPC.

Principal Diseases	Cases	Agreement
Fulminant hepatitis	3	3
Liver cirrhosis	5	5
Neoplastic metastasis to the liver	29	28
Cholangioma	6	5
Hepatoma	8	6
Liver abscess	1	1
Renal failure	2	2
Miscellaneous	1	1
	55	51 (92.7%)

Current Status of CALD and Its Future

Since 1949 we have been devoting ourselves to the development of a diagnostic system based solely on the interpretation of test results, a system which would enable us to appraise a patient's general condition and functional disturbances of major vital organs of the body, and, if possible, to list the names of his or her possible diseases without any supportive information regarding morbid history and the findings of physical examinations.[10–12] In the course of this investigation, in the late 1960s, the computer attracted our attention as a promising and useful tool for our purpose. It was in 1970 that we successfully used a computer to conprehensively interpret test results and print out the diagnosis of about 20 kinds of possible diseases and pathological conditions in our laboratory in Ube.[13] The medical records of patients with various diseases were checked for their blood spectrums.[11,12] Determination values of various blood chemical ingredients of the blood spectrum were individually examined for the range of variation in each of the diseases. The variation ranges thus obtained were collected and arranged individually by the blood spectrum pattern of the different diseases to identify the characteristic blood chemical features of

each disease. This was done in much the same manner as a physician's contemplation in making a clinical diagnosis. Characteristic blood chemical features were converted into diagnostic codes (Dx code)[14,15] for use in computer software. The diagnostic codes were classified according to the various diseases. Since 1970, these diagnostic codes (Dx codes) have been improved and have increased in number. At present, about 180 of them are kept in our laboratory. These Dx codes are not the elaborate end-products of mathematics, but rather are the fruits harvested from the thinking process in clinical diagnosis

Recently, independent of our team, Niwa[19] and his associates developed the SDI system of CALD at Tokai University Medical School Hospital. They measured 20 serum chemical ingredients (i) in a SMAC automation assembly, and expressed estimations (X_{pi}) in terms of standard deviations of the measurement of relevant chemical ingredients in the sera of normal subjects (SD_{ni}) to calculate their standard deviation index (SDI_i), which refers to deviation of any one of the ingredients from the normal average value (X_{ni}) by the following equation

$$SDI_i = \frac{X_{pi} - X_{ni}}{SD_{ni}}.$$

The SDI_i may be modified by the weight of diagnostic significance (WF_j) which is based on differences in diseases (j). A score (D_j) is calculated, for each disease (j), by summing up the weighted standard deviation index of 20 different serum chemical ingredients of patients by

$$D_j = \sum_{i=1\sim20}^{n} SDI_{ij} \times WF_{ij}.$$

The magnitude of the score (Dj) depends on difference in diseases. Accordingly, the names of possible diseases can be guessed by collation of the patient's score with the score table of diseases installed in the computer software. All calculations and collations are performed by a computer.

As in Japan, computers were first introduced into clinical laboratories in the United States in the 1960s. Initially, they were employed for clerical work, data acquisition and business functions, and their application to clinical diagnostic interpretation of laboratory data was slow. Essentially, this was because laboratories were staffed mostly by clinical chemists who, since they were not physicians, attached more importance to the rapidity, precision and accuracy of reported estimations than to the possibilities for clinical diagnosis. However, in the early 1970s, computers began to be used for clinical interpretation in several areas of laboratory work,[20] for instance, in analyses of the blood gas-pH system and the EMIT measurement system for antiepileptic drugs, in guessing deviations of estimations due to concomitant drugs, and in electrophoretic estimation of serum protein fractions. Mathematical theories of branching logic, decision trees, Bayes' theorem, discriminant function, etc. were utilized at this time in the preparation of computer software.[20]

Trials of CALD in the strict sense were scarce. Reece and Hobbie,[21] however, published the first instance of computerized interpretation of laboratory tests for clinical diagnosis in 1972. They connected an automated chemical analyzer, SMA 12/60, to an on-line computer and successfully received a print on report sheet paper of possible clinical diagnoses in the order of larger

probabilities. Button and Gambino (1973)[22] examined the CALD system employed by Reece and Hobbie and confirmed its usefulness for the diagnosis of hepatobiliary diseases, but found that it was unsatisfactory for the differential diagnosis of pneumonias, malignancies and infections. The Reece-Hobbie CALD system was continuously improved, and by 1981, it had evolved the level that it could issue two report sheet pages.[23] The estimation values of 23 chemical ingredients in serum, hematological tests (CBC and peripheral blood picture), and urinalyses were printed out together with their normal ranges, on the first page, while possible diagnoses were listed on the second page. This CALD has also been applied to the diagnostic interpretation of other tests such as those concerned with cytology and bacteriology (bacterial cultures and sensitivity to antibiotics). At present, the diagnostic interpretation of test results by means of computer is gradually expanding its area of utility. It has, for example, been employed with tests for diseases of the thyroid gland, the parathyroid gland, bone (metabolic diseases), and the liver.[20] Other tests including LDH isozyme studies, complete peripheral blood counts (CBC), gastric juice analyses, glucose tolerance tests and tests administered during clinical course follow-ups have also been subjected to clinical interpretation by computer.[23]

However, as pointed out by Young (1976),[20] CALD is still in its infancy. It's routine service has been restricted to a very small number of clinical laboratories. Elevitch (1982)[24] observed that CALD reports have been welcome by private clinics treating chiefly outpatients, but not so much favored in hospital settings where the attention of medical staffs is mainly given to inpatients. Currently the diagnostic hit rate of CALD (the chance of a successful diagnosis being made from among the five possible diseases of larger probability pointed out by a computer) is around 70 per cent generally,[24] and 90 per cent for hepatobiliary diseases.[20] These hit rates, however, can undoubtedly be raised within the next ten years if there is more successful cooperation between clinical pathologists working in laboratories and the medical staffs in charge of both inpatients and outpatients. Thus we believe that the future development of CALD systems is an important task facing both clinical pathologists and medical staffs.

REFERENCES

1) Laennec, R.T.H. : Traité de l'auscultation médiate et des maladies des poumons et du coeur. Paris, Chaudé. 1826
2) Hiraide, J. : Hypoproteinemia? Anemia? (Our proposal of criteria for appraisal of nutritional state, and its theoretical and experimental basis). Nisshin-Igaku **35** : 10-18, 1948 (in Japanese)
3) Ueda, H., Takeuchi, S. and Tanaka, G. : Plasma protein and blood hemoglobin as criteria for appraisal of nutritional state. Nippon Naika-Gakkai-Zasshi **38** : 47-51, 1949 (in Japanese)
4) Satake, K. : Studies on hypoproteinemia (Report 1). Nippon Naika-Gakkai-Zasshi **39** : 28-35, 1950 (in Japanese)
5) Ueda, H., Takeuchi, S. and Satake, K. : Hypoproteinemia (Report 2). Nippon Naika-Gakkai-Zasshi **39** : 333-339, 1950 (in Japanese)
6) Ueda, H., Takeuchi, S., Satake, K., Hirata, K. and Inoue, I. : Hypoproteinemia (Report 3). Nippon Naika-Gakkai-Zasshi **39** : 375-381, 1951 (in Japanese)
7) Muto, Y. : Nutritional assessment in internal medicine. Clinician **31** : 5-9, 1984 (in Japanese)
8) Vorhaus, L.J. and Kark, R.M. : Serum cholinesterase in health and disease. Am. J.

Med. **14** : 707–719, 1953
9) Shibata, S., Ueda, S. and Matsuda, N. : Clinical diagnosis by blood chemical analysis. Its principle and discipline. Tokyo, Igaku-shoin. 1984 (in Japanese)
10) Shibata, S. : Chemical diagnosis. Chiryo **31** : 247–257, 1949 (in Japanese)
11) Shibata, S. : Blood spectrum, a system of graphical representation of twelve chemical constituents of blood for the purpose of clinical diagnosis. Bull. Yamaguchi Med. Sch. **3** : 27–49, 1955
12) Murata, K. : Studies on blood spectrum. I, II and III. Bull. Yamaguchi Med. Sch. **4** : 37–54, 55–72, 73–100, 1956
13) Shibata, S., Ueda, S., Kameoka, M., Yonehara, Y., Miyaji, T., Fukuda, T., Maeda, M. and Koshikawa, Y. : Interpretation of routine laboratory test results by a computer. The 17th General Meeting (in Niigata) of the Japan Society of Clinical Pathologists, 1970
14) Shibata, S. : Current status of computer assisted laboratory diagnosis in Japan. Korean J. Clin. Pathol. **5** : 245–255, 1985
15) Matsuda, N. and Koresawa, S. : Computerized interpretation of blood chemical and hematological test results for clinical diagnosis. Rinsho-Byori **31** : 514–520, 1983
16) Shibata, S. : Some thoughts on laboratory examination. Asian Med. J. **27** : 277–285, 1984
17) Bennett, J.M., Catovsky, D., Daniel, M.T., Frandrin, G., Galton, D.A.G., Gralnick, H.R. and Sultan, C. : Proposal for the classification of the acute leukemias. Br. J. Haematol. **33** : 451–458, 1976
18) Shibata, S. : Dynamic hematology, illustrated. Leukocytes-infection, immunity and neoplasm. Kyoto, Kimpodo. 1984
19) Niwa, M. : Interpretation of patho-physiological states by laboratory data. Nippon Rinsho-Kensa Jidoka Gakkai-shi (Jap. J. Clin. Lab. Autom.) **10** : 11–21, 1985 (in Japanese)
20) Young, D.S. : Interpretation of clinical chemical data with the aid of automatic data processing. Clin. Chem. **22** : 1555–1561, 1976
21) Reece, R.L. and Hobbie, R.K. : Computer evaluation of chemistry values : A reporting and diagnostic aid. Am. J. Clin. Pathol. **57** : 664–675, 1972
22) Button, K.F. and Gambino, S.R. : Laboratory diagnosis by computer. Comput. Biol. Med. **3** : 131–136, 1973
23) Hobbie, R.K. and Reece, R.L. : Interpretive reporting by computer. Hum. Pathol. **12** : 127–134, 1981
24) Elevitch, F.R. : Computer-assisted clinical laboratory interpretive reports. Lab. Med. **13** : 45–47, 1982