Interpretation of Lab Test Profiles

Ed Uthman, MD

Diplomate, American Board of Pathology

Last update 6 Jan 2002

The various multiparameter blood chemistry and hematology profiles offered by most labs represent an economical way by which a large amount of information concerning a patient's physiologic status can be made available to the physician. The purpose of this monograph is to serve as a reference for the interpretation of abnormalities of each of the parameters.

Reference ranges ("normal ranges")

Because reference ranges (except for some lipid studies) are typically defined as the range of values of the median 95% of the healthy population, it is unlikely that a given specimen, even from a healthy patient, will show "normal" values for all the tests in a lengthy profile. Therefore, caution should be exercised to prevent overreaction to miscellaneous, mild abnormalities without clinical correlate.

Units of measurement: America against the world

American labs use a different version of the metric system than does most of the rest of the world, which uses the *Système Internationale* (SI). In some cases translation between the two systems is easy, but the difference between the two is most pronounced in measurement of chemical concentration. The American system generally uses mass per unit volume, while SI uses moles per unit volume. Since mass per mole varies with the molecular weight of the analyte, conversion between American and SI units requires many different conversion factors. Where appropriate, in this paper SI units are given after American units. Dennis Jay, PhD, has kindly made available an online converter between SI and conventional units:

<http://dwjay.tripod.com/conversion.html>

The Analytes

Sodium

Increase in serum sodium is seen in conditions with water loss in excess of salt loss, as in profuse sweating, severe diarrhea or vomiting, polyuria (as in diabetes mellitus or insipidus), hypergluco- or mineralocorticoidism, and inadequate water intake. Drugs causing elevated sodium include steroids with mineralocorticoid activity, carbenoxolone, diazoxide, guanethidine, licorice, methyldopa, oxyphenbutazone, sodium bicarbonate, methoxyflurane, and reserpine.

Decrease in sodium is seen in states characterized by intake of free water or hypotonic solutions, as may occur in fluid replacement following sweating, diarrhea, vomiting, and diuretic abuse. Dilutional hyponatremia may occur in cardiac failure, liver failure, nephrotic syndrome, malnutrition, and SIADH. There are many other causes of hyponatremia, mostly related to

corticosteroid metabolic defects or renal tubular abnormalities. Drugs other than diuretics may cause hyponatremia, including ammonium chloride, chlorpropamide, heparin, aminoglutethimide, vasopressin, cyclophosphamide, and vincristine.

Potassium

Increase in serum potassium is seen in states characterized by excess destruction of cells, with redistribution of K^+ from the intra- to the extracellular compartment, as in massive hemolysis, crush injuries, hyperkinetic activity, and malignant hyperpyrexia. Decreased renal K^+ excretion is seen in acute renal failure, some cases of chronic renal failure, Addison's disease, and other sodium-depleted states. Hyperkalemia due to pure excess of K^+ intake is usually iatrogenic.

Drugs causing hyperkalemia include amiloride, aminocaproic acid, antineoplastic agents, epinephrine, heparin, histamine, indomethacin, isoniazid, lithium, mannitol, methicillin, potassium salts of penicillin, phenformin, propranolol, salt substitutes, spironolactone, succinylcholine, tetracycline, triamterene, and tromethamine. Spurious hyperkalemia can be seen when a patient exercises his/her arm with the tourniquet in place prior to venipuncture. Hemolysis and marked thrombocytosis may cause false elevations of serum K^+ as well. Failure to promptly separate serum from cells in a clot tube is a notorious source of falsely elevated potassium.

Decrease in serum potassium is seen usually in states characterized by excess K^+ loss, such as in vomiting, diarrhea, villous adenoma of the colorectum, certain renal tubular defects, hypercorticoidism, etc. Redistribution hypokalemia is seen in glucose/insulin therapy, alkalosis (where serum K^+ is lost into cells and into urine), and familial periodic paralysis. Drugs causing hypokalemia include amphotericin, carbenicillin, carbenoxolone, corticosteroids, diuretics, licorice, salicylates, and ticarcillin.

Chloride

Increase in serum chloride is seen in dehydration, renal tubular acidosis, acute renal failure, diabetes insipidus, prolonged diarrhea, salicylate toxicity, respiratory alkalosis, hypothalamic lesions, and adrenocortical hyperfunction. Drugs causing increased chloride include acetazolamide, androgens, corticosteroids, cholestyramine, diazoxide, estrogens, guanethidine, methyldopa, oxyphenbutazone, phenylbutazone, thiazides, and triamterene. Bromides in serum will not be distinguished from chloride in routine testing, so intoxication may show spuriously increased chloride [see also "Anion gap," below].

Decrease in serum chloride is seen in excessive sweating, prolonged vomiting, salt-losing nephropathy, adrenocortical defficiency, various acid base disturbances, conditions characterized by expansion of extracellular fluid volume, acute intermittent porphyria, SIADH, etc. Drugs causing decreased chloride include bicarbonate, carbenoxolone, corticosteroids, diuretics, laxatives, and theophylline.

CO_2 content

Increase in serum CO_2 content for the most part reflects increase in serum bicarbonate (HCO_3^-) concentration rather than dissolved CO_2 gas, or $P_{CO\,2}$ (which accounts for only a small fraction of the total). Increased serum bicarbonate is seen in compensated respiratory acidosis and in metabolic alkalosis. Diuretics (thiazides, ethacrynic acid, furosemide, mercurials), corticosteroids (in long term use), and laxatives (when abused) may cause increased bicarbonate.

Decrease in blood CO_2 is seen in metabolic acidosis and compensated respiratory alkalosis.

Substances causing metabolic acidosis include ammonium chloride, acetazolamide, ethylene glycol, methanol, paraldehyde, and phenformin. Salicylate poisoning is characterized by early respiratory alkalosis followed by metabolic acidosis with attendant decreased bicarbonate.

Critical studies on bicarbonate are best done on anaerobically collected heparinized whole blood (as for blood gas determination) because of interaction of blood and atmosphere in routinely collected serum specimens. Routine electrolyte panels are usually not collected in this manner.

The tests "total CO_2" and "CO_2 content" measure essentially the same thing. The "$P_{CO\,2}$" component of blood gas analysis is a test of the ventilatory component of pulmonary function only.

Anion gap

Increased serum anion gap reflects the presence of unmeasured anions, as in uremia (phosphate, sulfate), diabetic ketoacidosis (acetoacetate, beta-hydroxybutyrate), shock, exercise-induced physiologic anaerobic glycolysis, fructose and phenformin administration (lactate), and poisoning by methanol (formate), ethylene glycol (oxalate), paraldehyde, and salicylates. Therapy with diuretics, penicillin, and carbenicillin may also elevate the anion gap.

Decreased serum anion gap is seen in dilutional states and hyperviscosity syndromes associated with paraproteinemias. Because bromide is not distinguished from chloride in some methodologies, bromide intoxication may appear to produce a decreased anion gap.

Glucose

Hyperglycemia can be diagnosed only in relation to time elapsed after meals and after ruling out spurious influences (especially drugs, including caffeine, corticosteroids, estrogens, indomethacin, oral contraceptives, lithium, phenytoin, furosemide, thiazides, thyroxine, and many more). Previously, the diagnosis of diabetes mellitus was made by demonstrating a fasting blood glucose >140 mg/dL (7.8mmol/L) and/or 2-hour postprandial glucose >200 mg/dL (11.1 mmol/L) on more than one occasion. In 1997, the American Diabetes Association revised these diagnostic criteria. The new criteria are as follows:

- Symptoms of diabetes plus a casual plasma glucose of 200 mg/dL [11.1 mmol/L] or greater.

OR

- Fasting plasma glucose of 126 mg/dL [7.0 mmol/L] or greater.

OR

- Plasma glucose of 200 mg/dL [11.1 mmol/L] or greater at 2 hours following a 75-gram glucose load.

At least one of the above criteria must be met on more than one occasion, and the third method (2-hour plasma glucose after oral glucose challenge) is not recommended for routine clinical use. The criteria apply to *any* age group. This means that the classic oral glucose tolerance test is now obsolete, since it is not necessary for the diagnosis of either diabetes mellitus or reactive hypoglycemia.

Diagnosis of gestational diabetes mellitus (GDM) is slightly different. The screening test, performed between 24 and 28 weeks of gestation, is done by measuring plasma glucose 1 hour

after a 50-gram oral glucose challenge. If the plasma glucose is 140 mg/dL or greater, then the diagnostic test is performed. This consists of measuring plasma glucose after a 100-gram oral challenge. The diagnostic criteria are given in the table below.

Time	Glucose (mg/dL)	Glucose (mmol/L)
Fasting	105	5.8
1 hour	190	10.5
2 hours	165	9.2
3 hours	145	8.0

In adults, **hypoglycemia** can be observed in certain neoplasms (islet cell tumor, adrenal and gastric carcinoma, fibrosarcoma, hepatoma), severe liver disease, poisonings (arsenic, CCl_4, chloroform, cinchophen, phosphorous, alcohol, salicylates, phenformin, and antihistamines), adrenocortical insufficiency, hypothroidism, and functional disorders (postgastrectomy, gastroenterostomy, autonomic nervous system disorders). Failure to promptly separate serum from cells in a blood collection tube causes falsely depressed glucose levels. If delay in transporting a blood glucose to the lab is anticipated, the specimen should be collected in a fluoride-containing tube (gray-top in the US, yellow in the UK).

In the past, the 5-hour oral glucose tolerance test was used to diagnose reactive (postprandial) hypoglycemia, but this has fallen out of favor. Currently, the diagnosis is made by demonstrating a low plasma glucose (<50 mg/dL[2.8 mmol/L]) *during a symptomatic episode*.

Urea nitrogen (BUN)

Serum urea nitrogen (BUN) is **increased** in acute and chronic intrinsic renal disease, in states characterized by decreased effective circulating blood volume with decreased renal perfusion, in postrenal obstruction of urine flow, and in high protein intake states.

Decreased serum urea nitrogen (BUN) is seen in high carbohydrate/low protein diets, states characterized by increased anabolic demand (late pregnancy, infancy, acromegaly), malabsorption states, and severe liver damage.

In Europe, the test is called simply "urea."

Creatinine

Increase in serum creatinine is seen any renal functional impairment. Because of its insensitivity in detecting early renal failure, the creatinine clearance is significantly reduced before any rise in serum creatinine occurs. The renal impairment may be due to intrinsic renal lesions, decreased perfusion of the kidney, or obstruction of the lower urinary tract.

Nephrotoxic drugs and other chemicals include:

antimony	arsenic	bismuth	cadmium
copper	gold	iron	lead
lithium	mercury	silver	thallium
uranium	aminopyrine	ibuprofen	indomethacin
naproxen	fenoprofen	phenylbutazone	phenacetin

salicylates	aminoglycosides	amphotericin	cephalothin
colistin	cotrimoxazole	erythromycin	ampicillin
methicillin	oxacillin	polymixin B	rifampin
sulfonamides	tetracyclines	vancomycin	benzene
zoxazolamine	tetrachloroethylene	ethylene	glycol
acetazolamide	aminocaproic acid	aminosalicylate	boric acid
cyclophosphamide	cisplatin	dextran (LMW)	furosemide
mannitol	methoxyflurane	mithramycin	penicillamine
pentamide	phenindione	quinine	thiazides
carbon tetrachloride			

Deranged metabolic processes may cause increases in serum creatinine, as in acromegaly and hyperthyroidism, but dietary protein intake does not influence the serum level (as opposed to the situation with BUN). Some substances interfere with the colorimetric system used to measure creatinine, including acetoacetate, ascorbic acid, levodopa, methyldopa, glucose and fructose. Decrease in serum creatinine is seen in pregnancy and in conditions characterized by muscle wasting.

BUN:creatinine ratio

BUN:creatinine ratio is usually >20:1 in prerenal and postrenal azotemia, and <12:1 in acute tubular necrosis. Other intrinsic renal disease characteristically produces a ratio between these values.

The BUN:creatinine ratio is not widely reported in the UK.

Uric acid

Increase in serum uric acid is seen idiopathically and in renal failure, disseminated neoplasms, toxemia of pregnancy, psoriasis, liver disease, sarcoidosis, ethanol consumption, etc. Many drugs elevate uric acid, including most diuretics, catecholamines, ethambutol, pyrazinamide, salicylates, and large doses of nicotinic acid.

Decreased serum uric acid level may not be of clinical significance. It has been reported in Wilson's disease, Fanconi's syndrome, xanthinuria, and (paradoxically) in some neoplasms, including Hodgkin's disease, myeloma, and bronchogenic carcinoma.

Inorganic phosphorus

Hyperphosphatemia may occur in myeloma, Paget's disease of bone, osseous metastases, Addison's disease, leukemia, sarcoidosis, milk-alkali syndrome, vitamin D excess, healing fractures, renal failure, hypoparathyroidism, diabetic ketoacidosis, acromegaly, and malignant hyperpyrexia. Drugs causing serum phosphorous elevation include androgens, furosemide, growth hormone, hydrochlorthiazide, oral contraceptives, parathormone, and phosphates.

Hypophosphatemia can be seen in a variety of biochemical derangements, incl. acute alcohol intoxication, sepsis, hypokalemia, malabsorption syndromes, hyperinsulinism, hyperparathyroidism, and as result of drugs, e.g., acetazolamide, aluminum-containing antacids, anesthetic agents, anticonvulsants, and estrogens (incl. oral contraceptives). Citrates, mannitol,

oxalate, tartrate, and phenothiazines may produce spuriously low phosphorus by interference with the assay.

Calcium

Hypercalcemia is seen in malignant neoplasms (with or without bone involvement), primary and tertiary hyperparathyroidism, sarcoidosis, vitamin D intoxication, milk-alkali syndrome, Paget's disease of bone (with immobilization), thyrotoxicosis, acromegaly, and diuretic phase of renal acute tubular necrosis. For a given total calcium level, acidosis increases the physiologically active ionized form of calcium. Prolonged tourniquet pressure during venipuncture may spuriously increase total calcium. Drugs producing hypercalcemia include alkaline antacids, DES, diuretics (chronic administration), estrogens (incl. oral contraceptives), and progesterone.

Hypocalcemia must be interpreted in relation to serum albumin concentration (Some laboratories report a "corrected calcium" or "adjusted calcium" which relate the calcium assay to a normal albumin. The normal albumin, and hence the calculation, varies from laboratory to laboratory).

True decrease in the physiologically active ionized form of Ca^{++} occurs in many situations, including hypoparathyroidism, vitamin D deficiency, chronic renal failure, magnesium deficiency, prolonged anticonvulsant therapy, acute pancreatitis, massive transfusion, alcoholism, etc. Drugs producing hypocalcemia include most diuretics, estrogens, fluorides, glucose, insulin, excessive laxatives, magnesium salts, methicillin, and phosphates.

Iron

Serum iron may be **increased** in hemolytic, megaloblastic, and aplastic anemias, and in hemochromatosis, acute leukemia, lead poisoning, pyridoxine deficiency, thalassemia, excessive iron therapy, and after repeated transfusions. Drugs causing increased serum iron include chloramphenicol, cisplatin, estrogens (including oral contraceptives), ethanol, iron dextran, and methotrexate.

Iron can be **decreased** in iron-deficiency anemia, acute and chronic infections, carcinoma, nephrotic syndrome, hypothyroidism, in protein- calorie malnutrition, and after surgery.

Alkaline phosphatase (ALP)

Increased serum alkaline phosphatase is seen in states of increased osteoblastic activity (hyperparathyroidism, osteomalacia, primary and metastatic neoplasms), hepatobiliary diseases characterized by some degree of intra- or extrahepatic cholestasis, and in sepsis, chronic inflammatory bowel disease, and thyrotoxicosis. Isoenzyme determination may help determine the organ/tissue responsible for an alkaline phosphatase elevation.

Decreased serum alkaline phosphatase may not be clinically significant. However, decreased serum levels have been observed in hypothyroidism, scurvy, kwashiokor, achrondroplastic dwarfism, deposition of radioactive materials in bone, and in the rare genetic condition hypophosphatasia.

There are probably more variations in the way in which alkaline phosphatase is assayed than any other enzyme. Therefore, the reporting units vary from place to place. The reference range for the assaying laboratory must be carefully studied when interpreting any individual result.

Lactate dehydrogenase (LD or "LDH")

Increase of LD activity in serum may occur in any injury that causes loss of cell cytoplasm. More specific information can be obtained by LD isoenzyme studies. Also, elevation of serum LD is

observed due to in vivo effects of anesthetic agents, clofibrate, dicumarol, ethanol, fluorides, imipramine, methotrexate, mithramycin, narcotic analgesics, nitrofurantoin, propoxyphene, quinidine, and sulfonamides.

Decrease of serum LD is probably not clinically significant.

There are two main analytical methods for measuring LD: pyruvate->lactate and lactate->pyruvate. Assay conditions (particularly temperature) vary among labs. The reference range for the assaying laboratory must be carefully studied when interpreting any individual result.

Many European labs assay alpha-hydroxybutyrate dehydrogenase (HBD or HBDH), which roughly equates to LD isoenzymes 1 and 2 (the fractions found in heart, red blood cells, and kidney).

ALT (SGPT)

Increase of serum alanine aminotransferase (ALT, formerly called "SGPT") is seen in any condition involving necrosis of hepatocytes, myocardial cells, erythrocytes, or skeletal muscle cells. [See "Bilirubin, total," below]

AST (SGOT)

Increase of aspartate aminotransferase (AST, formerly called "SGOT") is seen in any condition involving necrosis of hepatocytes, myocardial cells, or skeletal muscle cells. [See "Bilirubin, total," below] Decreased serum AST is of no known clinical significance.

GGTP (GAMMA-GT)

Gamma-glutamyltransferase is markedly **increased** in lesions which cause intrahepatic or extrahepatic obstruction of bile ducts, including parenchymatous liver diseases with a major cholestatic component (e.g., cholestatic hepatitis). Lesser elevations of gamma-GT are seen in other liver diseases, and in infectious mononucleosis, hyperthyroidism, myotonic dystrophy, and after renal allograft. Drugs causing hepatocellular damage and cholestasis may also cause gamma-GT elevation (see under "Total bilirubin," below).

Gamma-GT is a very sensitive test for liver damage, and unexpected, unexplained mild elevations are common. Alcohol consumption is a common culprit.

Decreased gamma-GT is not clinically significant.

Bilirubin

Serum total bilirubin is **increased** in hepatocellular damage (infectious hepatitis, alcoholic and other toxic hepatopathy, neoplasms), intra- and extrahepatic biliary tract obstruction, intravascular and extravascular hemolysis, physiologic neonatal jaundice, Crigler-Najjar syndrome, Gilbert's disease, Dubin-Johnson syndrome, and fructose intolerance.

Drugs known to cause cholestasis include the following:

aminosalicylic acid	androgens	azathioprine	benzodiazepines
carbamazepine	carbarsone	chlorpropamide	propoxyphene

estrogens	penicillin	gold Na thiomalate	imipramine
meprobamate	methimazole	nicotinic acid	progestins
penicillin	phenothiazines	oral contraceptives	
sulfonamides	sulfones	erythromycin estolate	

Drugs known to cause hepatocellular damage include the following:

acetaminophen	allopurinol	aminosalicylic acid	amitriptyline
androgens	asparaginase	aspirin	azathioprine
carbamazepine	chlorambucil	chloramphenicol	chlorpropamide
dantrolene	disulfiram	estrogens	ethanol
ethionamide	halothane	ibuprofen	indomethacin
iron salts	isoniazid	MAO inhibitors	mercaptopurine
methotrexate	methoxyflurane	methyldopa	mithramycin
nicotinic acid	nitrofurantoin	oral contraceptives	papaverine
paramethadione	penicillin	phenobarbital	phenazopyridine
phenylbutazone	phenytoin	probenecid	procainamide
propylthiouracil	pyrazinamide	quinidine	sulfonamides
tetracyclines	trimethadione	valproic acid	

Disproportionate **elevation** of direct (conjugated) bilirubin is seen in cholestasis and late in the course of chronic liver disease. Indirect (unconjugated) bilirubin tends to predominate in hemolysis and Gilbert's disease.

Decreased serum total bilirubin is probably not of clinical significance but has been observed in iron deficiency anemia.

Total protein

Increase in serum total protein reflects increases in albumin, globulin, or both. Generally significantly increased total protein is seen in volume contraction, venous stasis, or in hypergammaglobulinemia.

Decrease in serum total protein reflects decreases in albumin, globulin or both [see "Albumin" and "Globulin, A/G ratio," below].

Albumin

Increased absolute serum albumin content is not seen as a natural condition. Relative increase may occur in hemoconcentration. Absolute increase may occur artificially by infusion of hyperoncotic albumin suspensions.

Decreased serum albumin is seen in states of decreased synthesis (malnutrition, malabsorption, liver disease, and other chronic diseases), increased loss (nephrotic syndrome, many GI conditions, thermal burns, etc.), and increased catabolism (thyrotoxicosis, cancer chemotherapy,

Cushing's disease, familial hypoproteinemia).

Globulin, A/G ratio

Globulin is **increased** disproportionately to albumin (decreasing the albumin/globulin ratio) in states characterized by chronic inflammation and in B-lymphocyte neoplasms, like myeloma and Waldenström's macroglobulinemia. More relevant information concerning increased globulin may be obtained by serum protein electrophoresis.

Decreased globulin may be seen in congenital or acquired hypogammaglobulinemic states. Serum and urine protein electrophoresis may help to better define the clinical problem.

T_3 uptake

This test measures the amount of thyroxine-binding globulin (TBG) in the patient's serum. When TBG is increased, T_3 uptake is decreased, and vice versa. T_3 Uptake does *not* measure the level of T_3 or T_4 in serum.

Increased T_3 uptake (decreased TBG) in euthyroid patients is seen in chronic liver disease, protein-losing states, and with use of the following drugs: androgens, barbiturates, bishydroxycourmarin, chlorpropamide, corticosteroids, danazol, *d*-thyroxine, penicillin, phenylbutazone, valproic acid, and androgens. It is also seen in hyperthyroidism.

Decreased T_3 uptake (increased TBG) may occur due to the effects of exogenous estrogens (including oral contraceptives), pregnancy, acute hepatitis, and in genetically-determined elevations of TBG. Drugs producing increased TBG include clofibrate, lithium, methimazole, phenothiazines, and propylthiouracil. Decreased T_3 uptake may occur in hypothyroidism.

Thyroxine (T_4)

This is a measurement of the total thyroxine in the serum, including both the physiologically active (free) form, and the inactive form bound to thyroxine-binding globulin (TBG). It is **increased** in hyperthyroidism and in euthyroid states characterized by increased TBG (See "T_3 uptake," above, and "FTI," below). Occasionally, hyperthyroidism will not be manifested by elevation of T_4 (free or total), but only by elevation of T_3 (triiodothyronine). Therefore, if thyrotoxicosis is clinically suspect, and T_4 and FTI are normal, the test "T_3-RIA" is recommended (this is not the same test as "T_3 uptake," which has nothing to do with the amount of T_3 in the patient's serum).

T_4 is **decreased** in hypothyroidism and in euthyroid states characterized by decreased TBG. A separate test for "T_4" is available, but it is not usually necessary for the diagnosis of functional thyroid disorders.

FTI (T_7)

This is a convenient parameter with mathematically accounts for the reciprocal effects of T_4 and T_3 uptake to give a single figure which correlates with free T_4. Therefore, **increased** FTI is seen in hyperthyroidism, and **decreased** FTI is seen in hypothyroidism. Early cases of hyperthyroidism may be expressed only by decreased thyroid stimulation hormone (TSH) with normal FTI. Early cases of hypothyroidism may be expressed only by increased TSH with normal FTI. Currently, the method of choice for screening for both hyper- and hypothyroidism is serum TSH only.

Modern methodologies ("ultrasensitive TSH") allow accurate determination of the very low concentrations of TSH at the phyisological cutoff between the normal and hyperthyroid states.

ASSESSMENT OF ATHEROSCLEROSIS RISK: Triglycerides, Cholesterol, HDL-Cholesterol, LDL-Cholesterol, Chol/HDL ratio

All of these studies find greatest utility in assessing the risk of atherosclerosis in the patient. Increased risks based on lipid studies are independent of other risk factors, such as cigarette smoking.

Total cholesterol has been found to correlate with total and cardiovascular mortality in the 30-50 year age group. Cardiovascular mortality increases 9% for each 10 mg/dL increase in total cholesterol over the baseline value of 180 mg/dL. Approximately 80% of the adult male population has values greater than this, so the use of the median 95% of the population to establish a normal range (as is traditional in lab medicine in general) has no utility for this test. Excess mortality has been shown not to correlate with cholesterol levels in the >50 years age group, probably because of the depressive effects on cholesterol levels expressed by various chronic diseases to which older individuals are prone.

HDL-cholesterol is "good" cholesterol, in that risk of cardiovascular disease decreases with increase of HDL. An HDL-cholesterol level of <35 mg/dL is considered a coronary heart disease risk factor independent of the level of total cholesterol. One way to assess risk is to use the total cholesterol/HDL-cholesterol ratio, with lower values indicating lower risk. The following chart has been developed from ideas advanced by Castelli and Levitas, *Current Prescribing*, June, 1977. It is not commonly cited in current literature, but I have never seen a specific refutation of its validity either.

		Total cholesterol (mg/dL)								
		150	185	200	210	220	225	244	260	300
HDL-chol (mg/dL)	25	####	1.34	1.50	1.60	1.80	2.00	3.00	4.00	6.00
	30	####	1.22	1.37	1.46	1.64	1.82	2.73	3.64	5.46
	35	####	1.00	1.12	1.19	1.34	1.49	2.24	2.98	4.47
	40	####	0.82	0.92	0.98	1.10	1.22	1.83	2.44	3.66
	45	####	0.67	0.75	0.80	0.90	1.00	1.50	2.00	3.00
	50	####	0.55	0.62	0.66	0.74	0.82	1.23	1.64	2.46
	55	####	0.45	0.50	0.54	0.60	0.67	1.01	1.34	2.01
	60	####	0.37	0.41	0.44	0.50	0.55	0.83	1.10	1.65
	65	####	0.30	0.34	0.36	0.41	0.45	0.68	0.90	1.35
	over 70	####	####	####	####	####	####	####	####	####

The numbers with two-decimal format represent the relative risk of atherosclerosis *vis-à-vis* the general population. Cells marked "####" indicate very low risk or undefined risk situations. Some authors have warned against putting too much emphasis on the total-chol/HDL-chol ratio at the expense of the total cholesterol level.

Readers outside the US may find the following version of the table more useful. This uses SI units for total and HDL cholesterol:

		Total cholesterol (mmol/L)								
		3.9	4.8	5.2	5.4	5.7	5.8	6.3	6.7	7.8
HDL-chol (mmol/L)	0.65	####	1.34	1.50	1.60	1.80	2.00	3.00	4.00	6.00
	0.78	####	1.22	1.37	1.46	1.64	1.82	2.73	3.64	5.46
	0.91	####	1.00	1.12	1.19	1.34	1.49	2.24	2.98	4.47
	1.04	####	0.82	0.92	0.98	1.10	1.22	1.83	2.44	3.66
	1.16	####	0.67	0.75	0.80	0.90	1.00	1.50	2.00	3.00
	1.30	####	0.55	0.62	0.66	0.74	0.82	1.23	1.64	2.46

	1.42	####	0.45	0.50	0.54	0.60	0.67	1.01	1.34	2.01
	1.55	####	0.37	0.41	0.44	0.50	0.55	0.83	1.10	1.65
	1.68	####	0.30	0.34	0.36	0.41	0.45	0.68	0.90	1.35
over	1.81	####	####	####	####	####	####	####	####	####

Triglyceride level is risk factor independent of the cholesterol levels. Triglycerides are important as risk factors only if they are not part of the chylomicron fraction. To make this determination in a hypertriglyceridemic patient, it is necessary to either perform lipoprotein electrophoresis or visually examine an overnight- refrigerated serum sample for the presence of a chylomicron layer. The use of lipoprotein electrophoresis for routine assessment of atherosclerosis risk is probably overkill in terms of expense to the patient.

LDL-cholesterol (the amount of cholesterol associated with low-density, or beta, lipoprotein) is not an independently measured parameter but is mathematically derived from the parameters detailed above. Some risk- reduction programs use LDL-cholesterol as the primary target parameter for monitoring the success of the program. The "desirable" level for LDL-cholesterol is less than 100 mg/dL.

A detailed statement on this subject is "Primary Prevention of Coronary Heart Disease: Guidance From Framingham", *Circulation* 97:1876-1887, 1998. The full text is available online, courtesy of the American Heart Association.

Triglycerides

Markedly **increased** triglycerides (>500 mg/dL) usually indicate a nonfasting patient (i.e., one having consumed any calories within 12-14 hour period prior to specimen collection). If patient is fasting, hypertriglyceridemia is seen in hyperlipoproteinemia types I, IIb, III, IV, and V. Exact classification theoretically requires lipoprotein electrophoresis, but this is not usually necessary to assess a patient's risk to atherosclerosis [See "Assessment of Atherosclerosis Risk," above]. Cholestyramine, corticosteroids, estrogens, ethanol, miconazole (intravenous), oral contraceptives, spironolactone, stress, and high carbohydrate intake are known to increase triglycerides. Decreased serum triglycerides are seen in abetalipoproteinemia, chronic obstructive pulmonary disease, hyperthyroidism, malnutrition, and malabsorption states.

RBC (Red Blood Cell) count

The RBC count is most useful as raw data for calculation of the erythrocyte indices MCV and MCH [see below]. **Decreased** RBC is usually seen in anemia of any cause with the possible exception of thalassemia minor, where a mild or borderline anemia is seen with a high or borderline-high RBC. **Increased** RBC is seen in erythrocytotic states, whether absolute (polycythemia vera, erythrocytosis of chronic hypoxia) or relative (dehydration, stress polycthemia), and in thalassemia minor [see "Hemoglobin," below, for discussion of anemias and erythrocytoses].

HEMOGLOBIN, HEMATOCRIT, MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration)

Strictly speaking, anemia is defined as a decrease in total body red cell mass. For practical purposes, however, anemia is typically defined as hemoglobin <12.0 g/dL and direct determination of total body RBC mass is almost never used to establish this diagnosis. Anemias are then classed by MCV and MCHC (MCH is usually not helpful) into one of the following categories:

- **Microcytic/hypochromic anemia** (decreased MCV, decreased MCHC)
  - Iron deficiency (common)

    - Thalassemia (common, except in people of Germanic, Slavonic, Baltic, Native American, Han Chinese, Japanese descent)
    - Anemia of chronic disease (uncommonly microcytic)
    - Sideroblastic anemia (uncommon; acquired forms more often macrocytic)
    - Lead poisoning (uncommon)
    - Hemoglobin E trait or disease (common in Thai, Khmer, Burmese,Malay, Vietnamese, and Bengali groups)
- **Macrocytic/normochromic anemia** (increased MCV, normal MCHC)
    - Folate deficiency (common)
    - B_{12} deficiency (common)
    - Myelodysplastic syndromes (not uncommon, especially in older individuals)
    - Hypothyroidism (rare)
- **Normochromic/normocytic anemia** (normal MCV, normal MCHC) The first step in laboratory workup of this broad class of anemias is a reticulocyte count. Elevated reticulocytes implies a normo-regenerative anemia, while a low or "normal" count implies a hyporegenerative anemia:
    - **Normoregenerative** normocytic anemias (appropriate reticulocyte response)
        - Immunohemolytic anemia
        - Glucose-6-phosphate dehydrogenase (G6PD) deficiency (common)
        - Hemoglobin S or C
        - Hereditary spherocytosis
        - Microangiopathic hemolytic anemia
        - Paroxysmal hemoglobinuria
    - **Hyporegenerative** normocytic anemias (inadequate reticulocyte response)
        - Anemia of chronic disease
        - Anemia of chronic renal failure
        - Aplastic anemia*

*Drugs and other substances that have caused aplastic anemia include the following:

amphotericin	sulfonamides	phenacetin	trimethadione
silver	chlordiazepoxide	tolbutamide	thiouracil
carbamazepine	chloramphenicol	tetracycline	oxyphenbutazone
arsenicals	chlorpromazine	pyrimethamine	carbimazole
acetazolamide	colchicine	penicillin	aspirin
mephenytoin	bismuth	promazine	quinacrine
methimazole	chlorothiazide	dinitrophenol	ristocetin
indomethacin	phenytoin	gold	trifluoperazine
carbutamide	perchlorate	chlorpheniramine	streptomycin
phenylbutazone	primidone	mercury	meprobamate
chlorpropamide	thiocyanate	tripelennamine	benzene

The drugs listed above produce marrow aplasia via an unpredictable, idiosyncratic host response in a small minority of patients. In addition, many antineoplastic drugs produce predictable, dose-related marrow suppression; these are not detailed here.

POLYCYTHEMIA

Polycythemia is defined as an increase in total body erythrocyte mass. As opposed to the situation with anemias, the physician may directly measure rbc mass using radiolabeling by ^{51}Cr, so as to differentiate polycythemia (absolute erythrocytosis, as seen in polycythemia vera, chronic hypoxia, smoker's polycythemia, ectopic erythropoietin production, methemoglobinemia, and high O_2 affinity hemoglobins) from relative erythrocytosis (as seen in stress polycythemia and dehydration). Further details of the work-up of polycythemias are beyond the scope of this monograph.

RDW (Red cell Distribution Width)

The red cell distribution width is a numerical expression which correlates with the degree of anisocytosis (variation in volume of the population of red cells). Some investigators feel that it is useful in differentiating thalassemia from iron deficiency anemia, but its use in this regard is far from universal acceptance. The RDW may also be useful in monitoring the results of hematinic therapy for iron-deficiency or megaloblastic anemias. As the patient's new, normally-sized cells are produced, the RDW initially increases, but then decreases as the normal cell population gains the majority.

Further online reading on hematology and red cell disease

Blood Cells and the CBC is an introduction to the morphology and function of the red cells, white cells, and platelets. Photomicrographs are included. The complete blood count (CBC) is also covered.

Anemia: Pathophysiologic Consequences, Classification, and Clinical Investigation is an introduction to anemia.

Nutritional Anemias and Anemia of Chronic Disease deals with anemias caused by iron, folate, and vitamin B_{12} deficiencies.

Hemolytic Anemias is concerned with anemias caused by red cells being destroyed faster than a healthy marrow can replace them.

Hemoglobinopathies and Thalassemias covers sickle cell disease, hemoglobins C and E, and alpha- and beta-thalassemias.

Understanding Anemia, my first book, is now available in hardback and paper. The publisher has kindly allowed me to post the full text of Chapter 1 online. You can access it through the book outline at this link. There is also a link to buy the book from online bookstores at a substantial discount. This book is aimed at general readers and presumes a knowledge of biology at the high school level, then builds from there.

Platelet count

Thrombocytosis is seen in many inflammatory disorders and myeloproliferative states, as well as in acute or chronic blood loss, hemolytic anemias, carcinomatosis, status post-splenectomy, post-exercise, etc.

Thrombocytopenia is divided pathophysiologically into production defects and consumption defects based on examination of the bone marrow aspirate or biopsy for the presence of megakaryocytes. Production defects are seen in Wiskott-Aldritch syndrome, May-Hegglin anomaly, Bernard-Soulier syndrome, Chediak-Higashi anomaly, Fanconi's syndrome, aplastic anemia (see list of drugs, above), marrow replacement, megaloblastic and severe iron deficiency anemias, uremia, etc. Consumption defects are seen in autoimmune thrombocytopenias (including ITP and systemic lupus), DIC, TTP, congenital hemangiomas, hypersplenism, following massive hemorrhage, and in many severe infections.

WBC (White Blood Cell) count

The WBC is really a nonparameter, since it simply represents the sum of the counts of

granulocytes, lymphocytes, and monocytes per unit volume of whole blood. Automated counters do not distinguish bands from segs; however, it has been shown that if all other hematologic parameters are within normal limits, such a distinction is rarely important. Also, even in the best hands, trying to reliably distinguish bands from segs under the microscope is fraught with reproducibility problems. Discussion concerning a patient's band count probably carries no more scientific weight than a medieval theological argument.

Granulocytes

Granulocytes include neutrophils (bands and segs), eosinophils, and basophils. In evaluating numerical aberrations of these cells (and of any other leukocytes), one should first determine the absolute count by multiplying the per cent value by the total WBC count. For instance, 2% basophils in a WBC of 6,000/μL gives 120 basophils, which is normal. However, 2% basophils in a WBC of 75,000/μL gives 1500 basophils/μL, which is grossly abnormal and establishes the diagnosis of chronic myelogenous leukemia over that of leukemoid reaction with fairly good accuracy.

Neutrophils

Neutrophilia is seen in any acute insult to the body, whether infectious or not. Marked neutrophilia (>25,000/μL) brings up the problem of hematologic malignancy (leukemia, myelofibrosis) versus reactive leukocytosis, including "leukemoid reactions." Laboratory work-up of this problem may include expert review of the peripheral smear, leukocyte alkaline phosphatase, and cytogenetic analysis of peripheral blood or marrow granulocytes. Without cytogenetic analysis, bone marrrow aspiration and biopsy is of limited value and will not by itself establish the diagnosis of chronic myelocytic leukemia versus leukemoid reaction.

Smokers tend to have higher granulocyte counts than nonsmokers. The usual increment in total wbc count is 1000/μL for each pack per day smoked.

Repeated excess of "bands" in a differential count of a healthy patient should alert the physician to the possibility of Pelger-Huët anomaly, the diagnosis of which can be established by expert review of the peripheral smear. The manual band count is so poorly reproducible among observers that it is widely considered a worthless test. A more reproducible hematologic criterion for acute phase reaction is the presence in the smear of any younger forms of the neutrophilic line (metamyelocyte or younger).

Neutropenia may be paradoxically seen in certain infections, including typhoid fever, brucellosis, viral illnesses, rickettsioses, and malaria. Other causes include aplastic anemia (see list of drugs above), aleukemic acute leukemias, thyroid disorders, hypopitituitarism, cirrhosis, and Chediak-Higashi syndrome.

Eosinophils

Eosinophilia is seen in allergic disorders and invasive parasitoses. Other causes include pemphigus, dermatitis herpetiformis, scarlet fever, acute rheumatic fever, various myeloproliferative neoplasms, irradiation, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, smoking, tuberculosis, coccidioidomycosis, idiopathicallly as an inherited trait, and in the resolution phase of many acute infections.

Eosinopenia is seen in the early phase of acute insults, such as shock, major pyogenic infections, trauma, surgery, etc. Drugs producing eosinopenia include corticosteroids, epinephrine, methysergide, niacin, niacinamide, and procainamide.

Basophils

Basophilia, if absolute (see above) and of marked degree is a great clue to the presence of myeloproliferative disease as opposed to leukemoid reaction. Other causes of basophilia include allergic reactions, chickenpox, ulcerative colitis, myxedema, chronic hemolytic anemias, Hodgkin's disease, and status post-splenectomy. Estrogens, antithyroid drugs, and desipramine may also increase basophils.

Basopenia is not generally a clinical problem.

Lymphocytes

Lymphocytosis is seen in infectious mononucleosis, viral hepatitis, cytomegalovirus infection, other viral infections, pertussis, toxoplasmosis, brucellosis, TB, syphilis, lymphocytic leukemias, and lead, carbon disulfide, tetrachloroethane, and arsenical poisonings. A mature lymphocyte count >7,000/μL is an individual over 50 years of age is highly suggestive of chronic lymphocytic leukemia (CLL). Drugs increasing the lymphocyte count include aminosalicyclic acid, griseofulvin, haloperidol, levodopa, niacinamide, phenytoin, and mephenytoin.

Lymphopenia is characteristic of AIDS. It is also seen in acute infections, Hodgkin's disease, systemic lupus, renal failure, carcinomatosis, and with administration of corticosteroids, lithium, mechlorethamine, methysergide, niacin, and ionizing irradiation. Of all hematopoietic cells lymphocytes are the most sensitive to whole-body irradiation, and their count is the first to fall in radiation sickness.

Monocytes

Monocytosis is seen in the recovery phase of many acute infections. It is also seen in diseases characterized by chronic granulomatous inflammation (TB, syphilis, brucellosis, Crohn's disease, and sarcoidosis), ulcerative colitis, systemic lupus, rheumatoid arthritis, polyarteritis nodosa, and many hematologic neoplasms. Poisoning by carbon disulfide, phosphorus, and tetrachloroethane, as well as administration of griseofulvin, haloperidol, and methsuximide, may cause monocytosis.

Monocytopenia is generally not a clinical problem.

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ACKNOWLEDGEMENT

Many thanks to Michael Gayler, FIBMS, DMS, CertHSm (MLSO2, Department of Chemical Pathology, Leicester Royal Infirmary) <gaylers@zetnet.co.uk> for the excellent review and comments, and for the labor of translating American to SI units.

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