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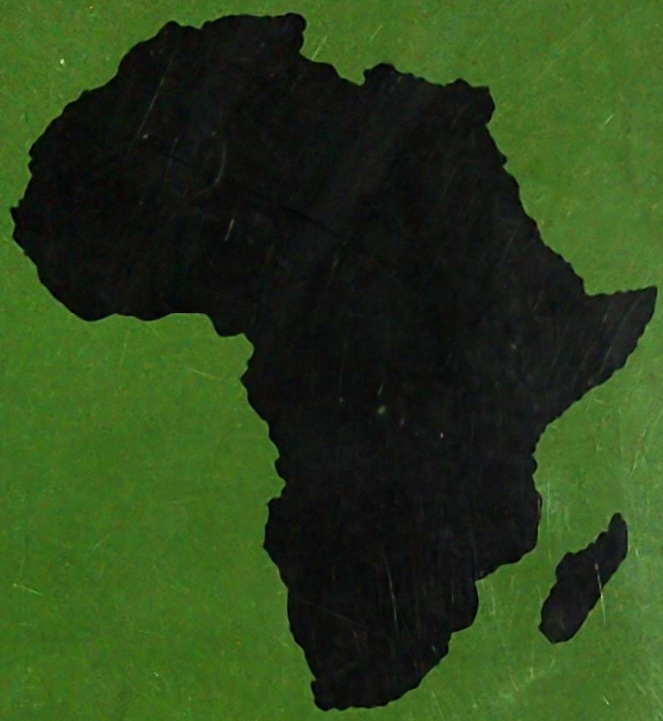

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Laboratory investigations in patient care*

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Abstract

The accurate diagnosis and management of disease almost always involves the judicious use of laboratory investigation. The increasing sophistication, diversity and expense of laboratory tests must however impose a moratorium on the use of these tests. This article reviews the justification for tests in clinical biochemistry and the general classes and varieties of tests available. Furthermore, factors that may make a test result normal or abnormal are discussed, with emphasis on the mechanisms, other than disease, that may have contributed to an unexpected result. The review ends with a discussion on the implications and modalities for extending clinical biochemical tests from the laboratories locations closer to the patient's bedside.

Résumé

Le diagnostique précis et le soin des maladies impliquent le plus souvent l'emploi judicieux de l'investigation au laboratorie clinique. Puisque les tests cliniques deviennent de plus en plus sophistiqués, divers et couteux, on propose un moratorium à l'usage de tels tests.

Cette communication analyse la justification des tests en biochimie clinique et établit les classes et les variétés des tests disponibles. En plus, elle discute les facteurs qui pourraient rendere normal ou anormal un test, mattant l'emphase sur les mécanismes, outre les maladies, qui pourraient encourager des résultats inattendus. L'analyse se termine par une discussion des implications de et les modalités nécessaires à apporter les tests cliniques biochimiques des laboratoires jusqu'auprès du chevet du patient.

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Introduction

Philosophically, there is really no need to justify the necessity for laboratory investigations in patient care. What may not be clear is the rationale behind the diagnostic value of any laboratory request. It is obviously not enough just to order specific investigations at specific times. Neither is it enough to justify investigations simply because they are 'routine' or 'I need the result for the next ward round just in case the Chief requests it'. Considerations of cost in human, material and technological terms must impose a moratorium on test requests.

The diagnostic process

There is a science to the art of medicine. There is method in the hunch, the flash of intuition, and the index of suspicion[1]. Much of this clinical method has to do with the particularisation to a specific patient, of our prior experiences with large numbers of other but similar patients. This ultimately results in a diagnosis: the effort to recognise the class or group to which a patient's illness belongs, so that based on the prior experience with that class, the subsequent clinical acts that can be carried out, and that the patient is willing to follow, it might be possible to ameliorate the patient's ill- health.

The essential steps in the diagnostic process are[2]:

i. establishment of diagnostic hypotheses followed by attempts to reduce their number by progressively ruling out specific diseases. This process requires very sensitive tests — if results are then normal, the physician can exclude the disease in question;
ii. pursuit of a strong clinical suspicion which

requires a specific test. When results are abnormal, the presence of disease is confirmed.

A test and the purpose of that test should match. The purpose of the test, moreover, should accurately reflect the doctor's estimate of the likelihood of disease based upon prior assessment to the available clinical information. The use of a test to exclude or confirm a diagnosis should indicate that the physician's best estimate after a careful evaluation of the patient's problem is that the diagnosis in question is either unlikely or probable. When the principles are followed, the conclusions reached from laboratory test results are likely to be correct and should lead to an appropriate action.

Types of laboratory tests

The ideal laboratory test should answer specific diagnosis and/or therapeutic questions. In general, such a test is either 'static' or dynamic/stress.

The 'static' test is performed on the patient as he presents clinically, and is the usual type of test e.g. routine fasting blood glucose, electrolytes and urea or liver function tests. These tests detect gross changes, but not minor ones which may have been compensated for, by the various homeostatic mechanisms. For example, the early type two diabetic patients may have normal fasting plasma glucose levels secondary to a compensatory hyperinsulinemia. Therefore, to investigate minimal disease, it is necessary to test the specific function while the patient is stressed.

This dynamic test also helps in determining the physiological level of an abnormality. There are three main types:

(a) loading the patient with a normal metabolite as with glucose in the OGTT or with ammonium chloride in testing renal acidification with suspected renal tubular acidosis;
(b) assessing the reserve ability of a target organ to respond to a hormonal stimulus e.g. TRH or LHRH tests for thyrotrophic and gonadotrophic activity respectively;
(c) to test the integrity of a feedback mechanism as in the metyrapone and dexamethasone suppression tests in assessing adrenocortical activity.

Laboratory investigations in patient care

There are two broad categories of laboratory investigations in patient care:

i. Screening tests

These tests are done on an apparently healthy population or otherwise, on admission, for all new patients, even when asymptomatic for the disorder in question. The aims of these tests are to [3]:

(a) detect those diseases whose morbidity and mortality can be reduced by early detection and treatment e.g. diabetes, hypertension, sickle cell disease, neonatal hypothyroidism.
(b) reassure patients found to be free of the disease (or the worse alternative of agitating patients with the pre-symptomatic disease for whom little can be done) e.g. AIDS.

It is unnecessary and unwise to screen for all possible diseases, even if human and technological resources allow. There must be guidelines defined to select appropriate patients and tests for early disease detection. These guidelines should include [4]:

i. the disease in question must be common enough to justify its detection;
ii. the disease must be accompanied by significant morbidity and mortality if not treated;
iii. effective therapy must exist to alter the natural history of the disease;
iv. detection and treatment in the presymptomatic state should result in benefits beyond those obtained through treatment of the early symptomatic patient.

An acceptable screening test should give abnormal results in almost all individuals with the disease. The physician should be fairly confident that the patient is free of the disease when results are normal e.g. OGTT in the diagnosis of diabetes, and, haemoglobin electrophoresis for haemoglobin SS disease. Specificity is important when screening for rare diseases, because of the implications of false positive results when the test is non-specific.

ii. Diagnosis tests

Diagnostic tests are commonly requested to [4]:

1. monitor the status of a disease process (cause, progression, stability, resolution);
2. identify and reverse complications of the disease and/or its treatment including drug toxicity;
3. ensure therapeutic levels of one or more drugs;
4. aid in assessing prognosis;
5. check on an unexpected tests or procedure result.

The frequency of testing will depend on:

i. a knowledge of the disease, its potential treatment complications, effective drug levels etc;
ii. awareness of factors other than disease that may influence the test result;
iii. application of principles of normal physiology, knowledge of expected rate of change of underlying disease and tests or procedures used to monitor the disease. For example, daily electrolytes and urea measurement in a hospitalised patient with normal renal function is unnecessary, as daily chest X- rays in a patient with uncomplicated pneumococcal pneumonia or weekly glycated haemoglobin determinations in the stable diabetic patient. On the other hand, tests may need to be requested hourly e.g. on the unstable shocked dialysed patient, or in a patient in diabetic coma.

Test interpretation

A test cannot be interpreted properly without considering the estimate of the likelihood of disease before the test result is obtained. When the pretest likelihood of disease is high, a positive result tends to confirm, but an unexpected negative result is not particularly helpful in ruling the disease out [5]. When the pretest likelihood of disease is low, a negative result tends to exclude but an unexpectedly positive result is not particularly helpful in confirming the disease. It is probable that physicians, in general, are more likely to render a diagnosis when a test result is unexpectedly abnormal than to reject a presumptive diagnosis when the confirmatory test result is normal.

A. The normal result

A normal test result may accomplish more than simply to reduce the likelihood of a specific disease. If two or more diseases are being considered and the same test is used for both and the sensitivity of that test for one is significantly different from that of the other, a normal reading may result in a major revision of the estimates of the likelihood of each disease. For example, anaemia may be suspected to be due to either iron deficiency or chronic disease. Red blood cell (RBC) indices are reduced in 90% of cases of iron deficiency and only 25% of cases of chronic disease. A finding of normal RBC indices would thus make chronic diseases more likely in this case.

There are however other considerations in interpreting the 'normal' result. These include [6]:

i. the normal range excludes about 2.5% of subjects whose values lie at the extremes of the distribution curve;
ii. for most measurable substances, distribution of test results is not normal but skewed, so that a normal range does not precisely define the central 95% of the subjects. However data can be log-transformed to achieve distribution normality;
iii. the reference population may not necessarily be free of disease, although it is theoretically possible to dilute the effects of disease by using large subject numbers — this further broadens the normal limits;
iv. few laboratories adjust the normal range for extra- disease factors that may influence the test result. These factors include age (plasma urea rises while alkaline phosphatase falls with increasing age), sex (variations in sex hormones, plasma urate and iron), weight (creatinine clearance depends on body surface area), race and geographical factors (Africans tend to have lower plasma cholesterol and fasting blood glucose than Caucasians), diet (fasting or postprandial, as with plasma glucose, triglycerides), time of day (cortisol and growth hormone exhibit a circadian rhythm), physical activity (stress hormones increase with exercise), position of the subject when blood was drawn (concentrations of plasma proteins and of substances bound to them are lower in the supine compared to the erect position), differing methods of biochemical analyses (e.g. enzymatic versus reductive methods for glucose estimation).
v. the uniform method used to define the normal range does not recognise the multiple purposes that the test may serve e.g. for diabetes, different plasma glucose levels are used for confirming the disease, excluding the disease or identifying a level beyond which specific treatment for the disease should be instituted. These parameters may vary between physicians, based on individual experience.

B. The abnormal result

An abnormal result may be clinically probable or improbable. Where the result is improbable, the test should be repeated. When this repeat test again gives an abnormal result similar to the earlier result, it is necessary to investigate the source of this

improbability. It could of course merely indicate an error or oversight in clinical judgment. On the other hand, it could be due to errors in the process of obtaining the samples of transferring the specimens to the laboratory [7]. Common examples of inadvertent errors resulting in spuriously abnormal results are [8,9]:

i. *Effects of procedures before venepuncture.* These include —
   - — *effects of drugs* e.g. unexpected hypokalaemia after taking thiazide diuretics);
   - — *effects of interfering substances* e.g. high bilirubin levels interfere with the Jaffe creatinine assay methods, drugs such as salicylates compete with thyroxine for TBG binding and may thereby falsely lower plasma thyroxine levels;
   - — *effects of intravenous infusions*: low plasma sodium may be due to hyperlipidemia and/or hyperproteinaemia (e.g. after intravenous hyperalimentation);
   - — *effects of clinical procedures*: plasma acid phosphatase levels rise after prostatic palpation and this rise may persist for many days.

ii. *Effects of the technique of venepuncture.* These are:
   - — *effects of venous stasis:* plasma total protein, albumin, haemoglobin and calcium levels rise with prolonged tourniquet application during venepuncture. Also prolonged stasis causes local hypoxia with leakage of intracellular constituents such as potassium and phosphate from the cellular elements into plasma with consequently high plasma levels.
   - — *effect of site of venepuncture*: blood should not be drawn from a vein receiving an i.v. infusion. The effects on results can only be imagined.
   - — *effects of inadequate containers:* blood for glucose assay should be in a fluoride container; it is also better to assess potassium from plasma rather than serum since potassium may be released during clotting; calcium should not be collected in oxalate treated tubes and potassium measurements from a specimen collected in a K-EDTA tube will be useless.
   - — *effects of poor storage and haemolysis of blood:* blood specimens that cannot be analysed immediately should be stored in a refrigerator for not longer than 24 hr or spun down and the plasma/serum frozen. Otherwise, haemolysis will increase the plasma concentrations of such intracellular constituents as potassium, phosphate and enzymes (e.g. LDH, AST).

Similar precautions need to be taken for other analytes especially stool and urine. Where timed specimen collection is indicated e.g. 24hr. urine for creatinine clearance estimation or 3-day faecal samples for faecal fat analysis, efforts should be taken to ensure proper timing, as carelessness may invalidate results, after so much effort and inconvenience might have been expended on specimen collection. In all cases, specimens should be properly labelled with names, origin of request, dates, time of collection and test required. The accompanying request form should also give enough information to the laboratory (including diagnosis) to ensure that the laboratory personnel, on getting an unexpected result, can activate the appropriate quality control mechanisms and recheck such a result. It may also necessitate that the laboratory personnel contact the requesting physician for clarifications on areas of uncertainty.

Clinical investigations nearer to the patient

This discussion cannot be complete without mentioning the importance of bedside laboratory tests. A variety of strips and tablets and other immobilised reagents are available for these procedures. Traditionally, these tests are carried out by nursing and/or medical personnel in the ward side rooms. Recently, pharmacy shops or even patent medicine shops in Nigeria, have started providing these services. In other parts of the world, supermarkets offer such diagnostic services; such advertisement signs as "Measure your weight, height, blood pressure and blood cholesterol for only $5.00", or "Test your urine while you wait" or "Instant Pregnancy Tests" are commonly displayed. Judging by the trend of events, very soon, there will be "Instant AIDS Tests". Although these are yet futuristic in Nigeria, it can be only a matter of time before the bigger shops in the major Nigerian urban centres, begin offering such services. The enormous ethical implications aside, whether for the trained doctor or for the charlatan, there must be some

considerations in interpreting results of such 'instant' tests. These include [10]:

i. the possibility of untrained individuals handling potentially infected specimens;
ii. the difficulty of maintaining the quality and use of the immobilised reagents and machinery;
iii. poor quality control and hence difficulty in obtaining correct results or accepting such results as correct;
iv. lack of immediate access to trained medical personnel to accurately interprete test results especially in cases of false positives, or offer counsel when results are true positives particularly with the 'instant' AIDS and cholesterol tests.

However there can be no doubt that these bedside tests can offer tremendous immediate diagnostic information in the right hands with appropriate reagents and expert help. Big pathology units should always oversee the required quality control and offer needed backup support and supervision.

Conclusion

It is important, in concluding, to define the qualities of the ideal diagnostic test, and for this, the poem written by Professor Baron [11], appears most apt:

The ideal diagnostic test:
can be done at the bedside;
painless for the patient;
free of risk;
quick and easy;
does not need great skill;
inexpensive equipment;
low cost of reagents;
accurate and precise;
sensitive and specific;
no false positives;
no false negatives;
high predictive values;
easy to interprete.

The only snag is that it does not exist.

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