Medicine in Old Age

Problems of Interpretation of Laboratory Findings in the Old

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Haematological, biochemical, and endocrine disorders are common in old age, and are often eminently remediable, but assessment of their significance is frequently hampered by problems of interpretation of the laboratory data on which the diagnosis and management of such disorders usually rest. There are several reasons for these difficulties in interpretation. Simple lack of knowledge of well-established normal values is not infrequent. Many normal values in the elderly are identical to those recognized for the young. If an abnormal value is mistakenly considered to be normal "for the patient's age," the opportunity for correct diagnosis and active treatment will be missed. Conversely some normal values differ in the elderly from those taught for the young. If a value normal for the patient's age is considered abnormal, then the patient may be subjected to unnecessary and possibly even hazardous further investigations—or an incorrect diagnosis and so perhaps prognosis will result. In both instances the necessary information may be found in journals which are not easily accessible, may not yet be in the textbooks, and in consequence is not taught.

A further difficulty arises from the fact that some normal values are not yet certainly established for the elderly. One reason for this is the high frequency of disease states in old age, which may make distinction of normal from abnormal uncertain. There is often in addition a problem in assessing the significance of minor deviations from normality as shown by laboratory tests in old people, and consequent difficulty in management of patients with such abnormalities.

The present paper attempts to review and discuss in respect of the elderly several commonly performed laboratory tests and the problems of interpretation which they present, both in relation to screening procedures and to the assessment of sick old people.

Haematological Tests

HAEMOGLOBIN CONCENTRATION

The haemoglobin concentration does not change significantly with age,¹ and thus values considered to indicate anaemia should be identical in young and old. If a haemoglobin concentration of less than 12 g/100 ml is taken to define anaemia,² or at least as an indication for further investigation, a few elderly women will be found whose haemoglobin concentration lies between 11.5 and 11.9 g/100 ml, yet who have no evident

cause for anaemia;³ and several men will be overlooked, whose haemoglobin concentration is above 12 g/100 ml, yet who have a definite and diagnosable abnormality remediable by treatment. Nevertheless, 12 g/100 ml is probably the best single level for the definition of anaemia in old age.

The standard haematological indices (P.C.V., M.C.H., M.C.H.C., M.C.V.) are unaffected by age, and so are the appearances of the blood film. A low M.C.H.C. and hypochromia should thus be taken to indicate iron deficiency, at least in the first instance, since this is the commonest single cause of anaemia in old age.³⁻⁵ Similarly a high M.C.V. and macrocytosis are evidence of the need to exclude a megaloblastic state due to deficiency of vitamin B₁₂ or folate.

SERUM IRON LEVELS

The serum iron tends to fall with age,⁵⁻⁶ so that levels as low as 50 µg/100 ml may be found when iron stores are adequate, as shown by the presence of substantial amounts in the bone marrow. The iron-binding saturation (serum iron as a percentage of total iron-binding capacity (T.I.B.C.)) is a more reliable index, since probably levels of 16% or below are not found when there are more than traces of iron in the bone marrow.⁷⁻⁸ Higher saturations may on occasion accompany undoubted iron deficiency, and the M.C.H.C. and blood film should always be taken into account. As many as 10% of elderly people living at home may have an abnormally low iron-binding saturation, but a normal haemoglobin concentration and a normal blood film.³ There is evidence that women of reproductive age who show a similar picture have a high chance of developing frank iron-deficiency anaemia within a few years,⁹ but whether the same is true of the elderly is not known. Since no symptomatic benefit accrues from the treatment of such people with iron,¹⁰⁻¹¹ there is at present no reason to treat such people with what has been termed "sideropenia without anaemia."

FOLATE AND B₁₂ LEVELS

Somewhat similar difficulties arise in the interpretation of serum folate levels in the elderly. Values as low as 1.5 ng/ml are often found in the absence of anaemia or neurological disorder.³⁻⁴ Again, there is no information about the prognostic significance of such levels, which would be considered abnormal in youth or middle age. A low serum vitamin B₁₂ level (below 140 pg/ml) can be taken to indicate deficiency of that vitamin as a cause of a megaloblastic anaemia in an old person, but low levels are also not uncommonly encountered in elderly people without anaemia, macrocytosis, or disorder of the nervous system.³ It is not yet known how frequently or how soon overt clinical disease may be expected to develop in such people, who may perhaps still possess hepatic stores of vitamin B₁₂ sufficient to last for long periods, but it is known that they are not benefited, in terms of symptoms, from vitamin B₁₂ therapy.¹²

WHITE CELL COUNT

The white cell count tends to fall with age, mainly owing to a reduction in lymphocyte count. Table I gives values derived from a study of 480 old people living at home.¹⁴ The upper limit of normal for the total white cell count is shown to be 9,000/mm³, which is less than the textbook figure of 10-11,000/mm³. Total counts over 9,000/mm³ may thus be taken to indicate leucocytosis. The lower limit of the total count is 3,000/mm³, and leucopenia should therefore not be diagnosed unless the count is below this figure, rather than the customary levels of 4-5,000/mm³. These two conclusions are good examples of the need for accurate knowledge of normal values in old age, to ensure correct diagnosis where this is appropriate, and to avoid unnecessary further investigation.

TABLE I—Range of normal values for the leucocyte count in people over 65 years of age¹⁴

	Absolute Count (cells/mm ³)	Differential Count (%)
Total	3,100-8,900	—
Polymorphs	1,800-6,500	45-85
Lymphocytes	700-3,500	10-50
Eosinophils	—	0-8
Monocytes	—	0-8

E.S.R.

Some uncertainty surrounds the interpretation of the erythrocyte sedimentation rate (E.S.R.) in old age. Studies to determine the true normal limits of this valuable simple test are difficult to carry out in the elderly, since even after the exclusion of acutely ill subjects, who constitute a high proportion of any hospital series, there remain many people with chronic conditions associated with an elevation of the E.S.R. Undoubtedly mean values rise steadily with age in healthy people, and are higher in women than men,¹⁵ and it is also clear that no convincing cause may be found in old people for values as high as 35-40 mm/hr.^{16 17} As in younger people, the isolated finding of a raised E.S.R. is best repeated after a few weeks, and only a persistent rise outside the limits mentioned should be regarded as an indication for further investigation.

Biochemical Tests

In many commonly performed biochemical tests mean normal values and the range encountered in relatively healthy old people are identical to those found in the young (table II). Abnormalities in these cannot therefore be attributed to ageing, but require assessment and diagnosis. The abnormalities most frequently met with are hypokalaemia,¹⁹ of which the commonest cause is diuretic drugs, and hypoalbuminaemia, which may be due to chronic infection, diffuse liver disease, or less often to simple malnutrition. The criteria for the identification of these abnormalities, and the action which should follow their detection, do not differ in essence in old age from standard practice in younger patients.

TABLE II—Normal Values for Biochemical Measurements in Old Age¹⁸

Measurement	Units	Mean $\pm$ S.D.	Range
Na ⁺	mEq/l	141 $\pm$ 3	135-146
K ⁺	"	4.4 $\pm$ 0.4	3.6-5.2
Cl ⁻	"	102 $\pm$ 3	96-108
HCO ₃ ⁻	"	25 $\pm$ 3	19-31
Total Protein	g/100 ml	7.1 $\pm$ 0.5	6.1-8.1
Albumin	"	4.1 $\pm$ 0.4	3.3-4.9
Globulin	"	3.1 $\pm$ 0.5	2.1-4.1
Mg ⁺⁺	mg/100 ml	2.0 $\pm$ 0.25	1.5-2.5
PO ₄ ⁻	M	3.1 $\pm$ 0.5	2.1-4.1
	F	3.4 $\pm$ 0.6	2.2-4.6
Bilirubin	"	*	0.3-1.5

*Lognormal frequency distribution.

BLOOD UREA AND CREATININE

For a second group of measurements the range of normal values is not the same in the elderly as in the young (table III). The most obvious example is the blood urea, which is the result of the body's production of the urea and the glomerular filtration rate. The former probably falls with age, and the latter certainly does,²⁰ and to a greater extent, so that the plasma concentration of urea rises with age.^{21 23} The upper limit of normal for the blood urea in people over 65 is about 60 mg/100 ml.²⁴ Renal failure, with its poor prognosis and attendant potentially hazardous investigations, should not be diagnosed if the blood urea is below this figure. Exactly similar considerations apply to the serum creatinine, for which a reasonable upper limit of normal in old age is 1.9 mg/100 ml, rather than the customary figure of 1.6 mg/100 ml.

TABLE III—Normal Values which differ in Old Age¹⁸

Substance	Units	Mean $\pm$ S.D.	Range
Urea	mg/100 ml	*	22-60
Creatinine	"	*	0.4-1.9
Cholesterol	M	*	160-345
	F	*	180-435
Ca ⁺⁺	M	9.5 $\pm$ 0.5	8.5-10.5
	F	9.7 $\pm$ 0.5	8.7-10.7
Uric acid	M	5.5 $\pm$ 1.2	3.1-7.9
	F	4.9 $\pm$ 1.4	2.1-7.7
Alkaline phosphatase	K-A units	*	5-20

*Lognormal frequency distribution.

URIC ACID, CHOLESTEROL, AND CALCIUM LEVELS

An age-related rise in serum uric acid is well-documented.^{25 26} Levels below 7.7 mg/100 ml should be regarded as normal (table III), and cannot be used to support a diagnosis of gout in an old person. The thiazide diuretics are the commonest cause of a rise of the serum uric acid level in old age.

The serum cholesterol concentration rises with age, and after the menopause is higher in women than in men, the reverse of the situation below that age.^{26 27} There may well be considerable local variation in normal levels in old age, associated with nutritional differences,²⁸ but in urban Scotland over 40% of women and 8% of men over the age of 65 have a serum cholesterol level of over 300 mg/100 ml.¹⁸ (Fig. 1). These high

Frequency distribution of serum cholesterol in old people living at home.¹⁸

values are not associated with coronary artery disease,²⁹ or with hypothyroidism, and only very high figures (of over 450 mg/100 ml or so) can be used to support the latter diagnosis in an old person. There is no evidence that lowering the serum cholesterol is of benefit to an elderly patient.

A further example of a normal range which may differ in old people is provided by the serum calcium. There seems little doubt that in elderly women the commonly accepted upper limit of 10.5 mg/100 ml is too low,^{18 26} and that values of 10.7 or even 11.0 mg/100 ml may be found in the absence of any symptoms or other biochemical or radiological evidence of hyperparathyroidism or other cause of hypercalcaemia. The sex difference shown in table III for serum calcium may perhaps be of clinical importance.

PHOSPHATASES

It is uncertain whether the normal range of serum alkaline phosphatase is the same in young and old. A rise in mean values with age has long been attributed to an age-related increase in the prevalence of Paget's disease, and more recently to osteomalacia since the recognition that this disorder is common in elderly women.³² Nevertheless, in elderly hospital patients, osteomalacia and Paget's disease are considerably less frequent conditions associated with a serum alkaline phosphatase above the conventional upper limit of normality of 15 King Armstrong units/100 ml than are liver disease, recent bone trauma, or malignant secondary deposits.³³ At present it would seem reasonable to regard a serum alkaline phosphatase of over 20 K-A units/100 ml as abnormal in an old person, and an indication for a search for liver or bone disease, and a value between 15 and 20 units as of uncertain significance. Values of over 50 units will usually be found to be due to Paget's disease, detectable either clinically or on a relatively restricted set of radiographs (for example, of the chest and pelvis), or to metastatic liver disease, of which there may be little other biochemical evidence. Determination of the iso-enzymes of alkaline phosphatase may be of great value, and wider availability of the test should help considerably in geriatric diagnosis.³⁴

Normal values for the serum acid phosphatase are usually considered to be the same in the elderly as in middle age, and measurement of the tartrate-labile fraction (with due caution that a rectal examination has not recently been performed) is of great value in the diagnosis and management of prostatic carcinoma, one of the controllable cancers. There is nothing to suggest any age-related difference in the concentrations of other commonly estimated serum enzymes, such as aspartate transaminase, alanine transaminase, or lactic dehydrogenase.

Tests of Endocrine Function

The endocrine disorders common in old age are diabetes mellitus, hyperthyroidism, and hypothyroidism. All others are distinctly rare, and only those tests relevant to the three common conditions mentioned will be discussed.

DIABETES

The most important single measurement in the diagnosis of diabetes is the random blood sugar. Values below 150 mg/100 ml may be accepted as normal in the elderly,^{17 35} and values over 200 mg/100 ml as indicative of diabetes—and thus requiring appropriate treatment. Most people with blood sugar levels over 200 mg/100 ml have glycosuria, and many have frank diabetic symptoms—though these may only come to light on direct questioning. The difficulties concern those elderly people found to have random blood sugar levels between 150 and 200 mg/100 ml. Consideration of all the circumstances, including the

presence or absence of symptoms, repetition of the random blood sugar, or determination of the fasting blood sugar (a value of 130 mg/100 ml or more being taken to indicate diabetes) will help in deciding whether a diagnosis of diabetes is justified. Recourse to a glucose tolerance test may only increase the uncertainties, since many old people have tests in the "borderline" region, with a blood sugar two hours after glucose between 120 mg/100 ml—the level defining normality—and 200 mg/100 ml—the level defining diabetes.

THYROID DISEASE

Of the numerous tests of thyroid function, those making use only of blood samples have much to recommend them in the diagnosis of thyroid disease in the elderly. The normal range of values of the serum protein-bound iodine (P.B.I.) is usually taken to be the same in old age as earlier in life (that is, 4-9 µg/100 ml), but the assessment of values outside this range, both below and above, is often made difficult by several factors which are common in the elderly. Acutely ill elderly patients often have low values of P.B.I., owing to reduction in thyroxine-binding globulin levels.³⁶ Falsely high values are perhaps even more frequent, and result from iodine ingestion (particularly in cough medicines), and from a variety of drugs.^{37 38} A careful drug history is thus essential in assessing the significance of an abnormal P.B.I. in an old person, but the use of the more recently introduced determinations of serum T-3 and T-4 levels is likely to be necessary to resolve many of these problems.³⁹ The greater availability of these tests will be of value in the diagnosis of these remediable disorders in old age.

Conclusion

Laboratory investigations are essential for the accurate diagnosis of many treatable conditions common in the elderly. The proper interpretation of the results of such investigations demands a knowledge both of the normal values encountered in old age and of the numerous factors which may produce misleading results.

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Any Questions?

We publish below a selection of questions and answers of general interest

Renal Tubular Acidosis

What is renal tubular acidosis? How can it be treated, and what is the prognosis?

Renal tubular acidosis (R.T.A.) is a selective defect in the kidney's ability to acidify the urine and leads to systemic acidosis. It must be distinguished from the acidosis that develops in renal failure, whatever the cause, when glomerular filtration rate (G.F.R.) falls to below 15-20 ml/min. In such advanced renal disease acidosis results from the reduction in the number of functioning nephrons. However, in R.T.A. the G.F.R. may be normal and nitrogen retention absent.

Several types of R.T.A. are recognized. In type 1 R.T.A. ("classic," "distal," or "gradient") the defect is believed to lie in an inability of the distal parts of the nephron to establish a normal gradient for hydrogen ion (H^+) between the tubular and peritubular fluids, possibly due to increased permeability of the tubular epithelium to H^+ . Urinary pH is inappropriately high for the systemic acidosis, with reduced plasma bicarbonate concentration, present in this condition. An "incomplete" form exists wherein the plasma bicarbonate level is normal but urinary pH cannot be lowered below about 5.8 in response to an acid load, usually given as ammonium chloride capsules.¹ Normally urine pH falls to 5.2 or less in these circumstances.

In type 2 R.T.A. ("proximal") the reabsorption of bicarbonate from proximal tubular fluid is defective. At normal plasma bicarbonate concentrations (that is, after correction of the acidosis) the urine contains a greater fraction of the filtered bicarbonate than in type 1. However, as acidosis becomes more marked in type 2 R.T.A. urine pH may fall to levels below those achievable in type 1 R.T.A. A definitive diagnosis of type 2 R.T.A. depends on a study of bicarbonate reabsorption by the tubules at varying filtered loads of bicarbonate.

Both types of R.T.A. may occur sporadically or in a genetically transmissible form in the absence of any detectable causal factors. However, both types may be produced by certain known agents or form part of various systemic diseases. Several excellent reviews exist.^{2,3} Both types of R.T.A. are characterized by hyperchloraemic acidosis with inappropriately high urine pH (but see above). Potassium deficiency due to renal potassium wastage is common in both types and a tendency towards sodium depletion also occurs. Nephrocalcinosis is common in type 1 but rare in type 2, whereas other evidence of disordered proximal tubular function such as aminoaciduria or glycosuria may be found in type 2 but not in type 1.

Treatment is limited to repairing the consequences of the renal dysfunction. Acidosis is treated with alkali—usually sodium bicarbonate, though Shohl's solution is much used in America. Type 1 R.T.A. is far more responsive to alkali therapy than type 2. Correction of acidosis usually leads to repair of the potassium deficit in type 1 but not in type 2. Potassium supplements, either chloride or citrate, are usually needed during correction of acidosis in both types of R.T.A. and the need for them continues thereafter in type 2. Treatment must be monitored by measurements of plasma electrolytes, especially HCO_3^- and K^+ .

If R.T.A. is not part of some serious generalized disorder or systemic disease the prognosis is in general good. However, some patients sustain progressive renal damage, usually associated with nephrocalcinosis, renal stones, and infection.

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Anticonvulsant Drugs and Hypocalcaemia

A woman aged 70 has been taking phenobarbitone 90 mg and phenytoin 100 mg daily for epilepsy over a period of 30 years. She has lately developed mild kyphosis. Is it advisable for her to take vitamin D?

Epileptic patients taking anticonvulsant drugs in high dosage over long periods may develop hypocalcaemia and, very rarely, rickets or osteomalacia.¹ Probably drug-mediated enzyme induction, mainly in the liver, causes a greatly increased inactivation of vitamin D. This disordered state may be corrected by vitamin D supplements and by ultraviolet ray irradiation. Correction of the drug-induced hypocalcaemia may lessen the frequency of seizures and thus decrease anticonvulsant drug requirements. It must be emphasized, however, that hypocalcaemia is a relatively uncommon complication of long-term anticonvulsant therapy, and if the patient in question has a normal plasma calcium, phosphorus, and alkaline phosphatase it is very unlikely that she has drug-induced osteomalacia. It is far more likely that she has senile osteoporosis, which would be unaffected by vitamin D supplements.

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