TABLE VII—*TSH versus F.T.I.: Distribution of Results in each Decision-aiding Range*

TSH (mU/l)	F.T.I. (nmol/l)					
	S1 (<38)	S2 (-77)	S3 (-118)	S4 (-176)	S5 (>176)	Total
0-11·5	7	216	60	6		289
-19·5	1	14	1			16
>19·5	10	28				38
Total	18	258	61	6	0	343

Tables V, VI, and VII show the futility of trying to widen or narrow the normal F.T.I. ranges to encompass all results so as to place them into their appropriate categories. This also highlights the need for replacing normal ranges with decision-aiding ranges.

Discussion

Let us consider two extremes: the doctor who thinks that thyrotoxicosis and hypothyroidism are clinical entities diagnosable on clinical grounds and that tests are a waste of effort; and the doctor who feels that thyrotoxicosis and hypothyroidism are states in which biochemical definition is essential because the clinical criteria are so often misleading. The former extreme is unlikely since only 13% of the request forms we saw contained a firm clinical diagnosis. The latter extreme is unlikely since attempts to define a range for normality and for disordered states founder on the continuous spectrum of thyroid disorder.

Since the essence of diagnosis is to determine the management that is best for the patient we devised a compromise strategy of defining "decision aiding ranges." Unlike computer-aided diagnosis,[15] the general principle of decision-aiding ranges relies on the current view of methods of diagnosis rather than the frequency distribution of disease which is needed for the Bayesian approach. Any doctor can set up his own strategy based on his own view of the diagnostic problem and the services offered by his laboratory.

The weakness in our study was the poor quality of the information on the request forms, but this may be overcome by designing request forms with coded clinical data. Thus, the numerical result may be correlated with the clinical state encoded in the request form through a set of rules for a technician or a computer program.[16] Also, the clinical acumen of the requester should be sharpened by having to record the clinical and treatment input accurately. The decision-aiding range strategy prevents all thyroid function tests to being requested at once. Our strategy is only one view of the state of thyroid function tests. Other strategies are equally valid and we are searching for one that will give the best results from the clinical, laboratory, and cost-effective view points.

We shall consider the effects of antithyroid and thyroid replacement treatment and pituitary disorders and endocrine exophthalmos on the strategy elsewhere. But, clearly, more complex decision-aiding ranges than those outlined here are needed for the appropriate evaluation of treatment. Nevertheless, our simple strategy for thyroid function assays reduced the clinical uncertainty in routine hospital practice from 47% to under 2%. For borderline raised F.T.I. results T-3 estimation was moderately successful but for borderline low results TSH estimation discriminated well between the euthyroid and the hypothyroid state.

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SHORT REPORTS

Hypervitaminosis A Accompanying Advanced Chronic Renal Failure

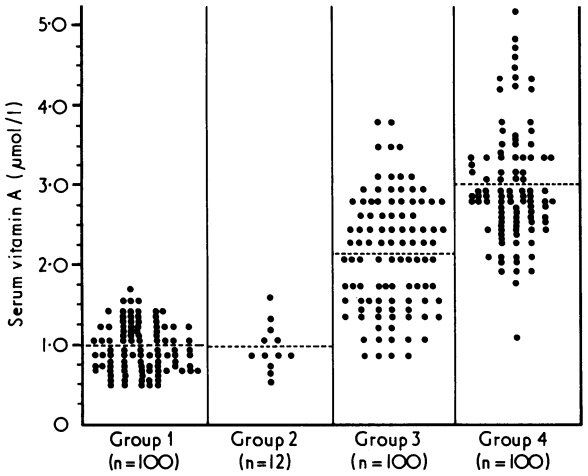
Many symptoms and lesions appearing in both experimental and clinical vitamin A intoxication (such as anorexia, nausea, vomiting, skin dryness, headache, pruritus, muscle fasciculation, peripheral paraesthesias, bleeding, and bone changes) are also common in severe uraemia. This prompted us to investigate serum vitamin A levels in patients with advanced renal failure.

Patients, Methods, and Results

We studied four groups of patients: group 1 consisted of 100 normal people (35 women and 65 men) aged between 20 and 61: group 2 of 12 patients (five women and seven men) aged between 20 and 68 with severe acute renal failure and serum creatinine over 884 μmol/l (10 mg/100 ml); group 3 of 100 patients (40 women and 60 men) aged between 18 and 52 with advanced chronic renal failure and serum creatinine constantly over 707 μmol/l (8 mg/100 ml); and group 4 of 100 patients (32 women and 68 men) aged between 16 and 64 undergoing regular chronic haemodialysis in five centres in Athens. Dialysis had lasted from six to 50 months using Ultra Flo 100, EX-01, or SP 75 R coil at a blood flow rate 250-350 ml/min three times a week (15-18 hours). The dialysate concentration of sodium was 135·0, acetate 35·0, chloride 102·0, calcium 1·75, magnesium 0·5, and potassium 1·5 mmol/l.

No subject had taken any hormones or vitamins for at least four months. Blood samples were taken after an overnight fast at 08.00 hours. All measurements were made in duplicate by the trifluoroacetic acid method (macroprocedure).[1]

The serum vitamin A results are summarized in the diagram. There was no significant difference between mean serum vitamin A in the controls (0·94±0·28 (0·03) μmol/l (27·75±8·10 (0·8) μg/100 ml)) and that in patients with acute renal failure (0·96±0·30 (0·08) μmol/l (27·50±8·57 (2·4) μg/100 ml) (t=0·09). In contrast the mean value was high in patients with advanced chronic renal failure (2·13±0·73 (0·07) μmol/l (60·93±21·0 (2·1) μg/100 ml) (t=15·0), and higher in patients undergoing chronic haemodialysis (3·00±0·72 (0·07) μmol/l (85·37±20·49 (2·0) μg/100 ml) (t=26·2). The difference in both groups was significant ($P<0·001$, and $P<0·001$, respectively).



Individual distribution of serum vitamin A levels. Horizontal lines represent means.

Discussion

It is not easy to account for the significant increase of serum vitamin A in patients with advanced chronic renal failure, which varied from two to five times the mean normal value. On the basis of some new concepts of vitamin A metabolism there are two hypotheses: (*a*) the increase may result from a previous rise in serum retinol-binding protein. The simultaneous increase of serum vitamin A and retinol-binding protein noted in patients suffering from renal disease[2] supports this possibility. Nevertheless, two of our patients had a liver vitamin A contents of 2·0 μmol/g and 2·24 μmol/g (585 and 642 μg/g)—values five times greater than in normal adults—which suggested that the whole body contained an excess of vitamin A. (*b*) The increase may be due to reduced excretion. Vitamin A is stored as retinol palmitate in the liver, from which it is liberated to maintain a normal level in the blood. Retinol is excreted in the bile after its transformation to retinoic acid together with glucoronide. Because retinoic acid seems to be formed in the kidney[3] the loss of renal tissue may cause a decreased production and, consequently, a reduced excretion of vitamin A derivatives.

What are the implications of this vitamin A accumulation in the patient with advanced renal failure? Such accumulation may play a role in the development of renal osteodystrophy. Two pathogenic mechanisms have been recognized in the development of renal bone disease: secondary hyperparathyroidism and vitamin D resistance. The most frequent lesions in clinical and experimental hypervitaminosis A occur in the bone, which is characterized by increased susceptibility to fractures. This is probably due to a direct action of vitamin A on the bone tissue leading to enhanced production of osteoclasts and increased bone resorption.[4] Alternatively, excess vitamin A may act on the parathyroid tissue, increasing the secretion of parathyroid hormone, perhaps through an interaction with the cell or secretion granule membrane.[5]

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Malignant Hypertension Presenting with an Acute Abdomen

Gastrointestinal tract vascular lesions are often found at necropsy in patients with malignant hypertension.[1 2] Two patients presenting with malignant hypertension and abdominal pain are described.

Case 1

A 21-year-old man was admitted after five weeks of increasing abdominal pain, headache, and failing eyesight. Blood pressure was 236/156 mm Hg, with bilateral haemorrhages, exudates, papilloedema, and retinal detachments. There was generalized abdominal tenderness with guarding.

Investigations: haemoglobin 10·7 g/dl, reticulocytes 4%, platelets 110×10^9/l. Blood films showed occasional irregularly contracted red cells, and fibrin degradation products were raised (40 mg/l). Serum sodium (134 mmol/l) and potassium (2·7 mmol/l) suggested secondary aldosterone excess, which was confirmed by raised plasma renin, 34 U/l (normal 4-18 U/l); angiotensin II, 69 pmol/l (5-35); and aldosterone, 370 ng/l (<18). Barium meal and follow-through showed a "cobble stone" appearance of distal ileum.

On intravenous diazoxide 300 mg blood pressure decreased (140/90 mm Hg). Laparotomy was performed on day 5 for increasing abdominal pain and signs of peritoneal inflammation; 60 cm of the distal ileum which showed oedema and haemorrhage of wall with patchy necrosis was resected. Histology showed fibrinoid necrosis of small arterioles.

Postoperative investigations, including intravenous pyelography, renal arteriography, and measurement of renal vein plasma renin showed no ause of hypertension though the right kidney was small (10 cm). Twelve months later blood pressure was well controlled with propranolol and the gross retinal lesions had healed.

Case 2

An 18-year-old girl was admitted after two weeks of back pain, headache, nausea and vomiting, and deteriorating eyesight. She had passed smoky red urine one week before admission. Six weeks earlier she had developed a sore throat which cleared spontaneously in three days. She had facial but no other peripheral oedema. Blood pressure was 220/150 mm Hg, with bilateral retinal haemorrhages, exudates, and papilloedema. The abdomen was tense with guarding and tenderness.

Investigations: haemoglobin 9·5 g/dl, reticulocytes 6%, platelets 40×10^9/l. Blood films showed occasional fragmented red cells. Antistreptolysin O was normal (100 U/l). There were red and white blood cells in the urine but no casts. Intravenous pentolinium 1 mg lowered the blood pressure (150/90 mm Hg). Continuous intravenous heparin (40 000 U/24 h) for three days produced no improvement. Laparotomy was performed on day 4 for increasing abdominal pain and 90 cm of necrotic distal ileum and ascending colon was resected. Histology showed patchy mucosal ulceration and thrombotic occlusions of small arteries with fibrinoid necrosis. Haemodialysis was needed for six weeks. After discharge at eight weeks blood pressure was poorly controlled despite intensive treatment. She was readmitted 12 months later in uraemia with malignant hypertension and microangiopathic haemolytic anaemia and died of gastrointestinal haemorrhage. At necropsy shrunken granular kidneys were found (right 30 g; left 130 g).

Comment

Both young patients presented in the malignant phase of hypertension with gastrointestinal lesions, gross retinopathy, and microangiopathic haemolytic anaemia. The cause of hypertension was not clear, though it may have been related in case 1 to an abnormal right kidney; but there was no clear evidence to support this or the possibility of a collagenosis. The second patient had features suggestive of acute glomerular nephritis though, not surprisingly, renal histology 12 months later showed no such evidence.

Though the aetiology of fibrinoid lesions in malignant hypertension is unknown the blood pressure level and the speed of its rise are probably important.[3] Fibrinoid lesions in the gut are common in animals with experimental hypertension.[4] In man, though minor gastrointestinal damage with identical arteriolar changes is often seen in patients dying with malignant hypertension,[1 2] major gut infarction has not been described. Abdominal pain with gut infarction associated with similar vascular lesions, however, has occurred in hypertensive patients after resection of an aortic coarctation.[3 5] That such abdominal symptoms are not seen more often is surprising in view of the dispersion of fibrinoid lesions in malignant hypertension.