AGEING AND ENDOCRINE FUNCTION

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Endocrine dysfunction in the elderly is characterised by its presentation in a setting of multiple system disorders and usually manifesting itself in an atypical and even subtle fashion. The consequences are two fold: problems are inevitably easily overlooked and there is rampant direct attribution of symptom complexes and signs to old age itself.

The Hypothalamic-Hypophyseal Axis

As confirmed by a multitude of basal and dynamic function tests and compounded by recent immunocytologic studies of ageing pituitaries, it is clear that the anterior pituitary maintains a practically intact production and secretion rate of its trophic hormones. What in fact varies is the amplitude of response to the hypothalamic releasing factors due to receptor insensitivity or a decrease in their concentration in the pituicyte membrane. There may also be a modification in the portal concentration of local neurotransmitter originating from the hypothalamus. I am emphasising two examples to illustrate this point:

(1) GROWTH HORMONE concentration is basally unmodified with advancing age but the sleep-entrained nocturnal peaks are much flatter as are the post-prandial increments of GH secretion, the response to aminoacid stimulation (e.g. arginine) and to the recently isolated and synthetic growth hormone releasing hormone (GRH).

(2) Similarly, PROLACTIN secretion is reduced post-menopausally but this is due to the fall in oestradiol with its prolactin stimulating as well as priming properties. It is no surprise to note that with Hormone Replacement Therapy, prolactin levels are normalised.

Superimposed on these examples, the centrally acting neurotransmitters are equally implicated: dopamine and the endogenous opiates exert an inhibitory tone on luteinising hormone releasing hormone and luteinising hormone secretion but in old age have reduced bioactivity and this explains the refractoriness of the gonadotrope to respond appropriately to negative feedback input by the circulating gonadal steroids.

Ageing is also characterised at this level by the preservation of anterior pituitary function and even more selectively, the corticotrophic axis which is the one most easily spared or more rapidly restored after hypothalamic-hypophyseal insult (including surgery) and this vis-a-vis the more fragile gonadotrope and thyrotrope lines. In fact, circulating levels of cortisol and adrenocorticotrophic hormone remain within the normal range in the elderly as do dynamic (stimulation and suppression) tests of the corticotrophic axis. The observed reduction in urinary 17-hydroxy corticosteroid levels is only an indication of diminished hepatic clearance of cortisol with subsequently prolonged half-life.

The modification of the gonadotrope axis is well known in women at the menopause which entails near complete absence of ovarian secretion of oestradiol as well as progesterone whereas circulating levels of testosterone and oestrone are preserved as a result of aromatisation in peripheral adipose tissue of $\Delta 4$ androstenedione whose origin is bifocal: ovarian and adrenal cortex.

The evolution of androgen secretion in old age is quite interesting albeit still widely disputed. Some authors describe a modification parallel to that of tri-iodothyronine (T3) whereby circulating testosterone levels are lowered only in chronically ill, debilitated, malnourished or alcoholic septuagenarians. However it is now thought that there is a progressive decline in total and free testosterone as well as dampening of their circadian fluctuations.

Hydro-electrolyte homeostasis is generally unaltered in normal elderly individuals such that plasma anti diuretic hormone (ADH) levels are generally normal. They and their precursor neurophysins may be occasionally above basal normal concentrations due to insensitivity of the distal nephron to anti diuretic hormone (ADH) and due to acquired increased responsiveness of the "osmostat" in the hypothalamus.

On the other hand, orthostatic hypotension is frequently encountered in old people due to diminished baroreceptor input to the supraoptic nucleus evidenced by an inadequate ADH response to volume depletion on assumption of the erect posture. The syndrome of inappropriate ADH secretion may be easily overlooked in the geriatric patient and the hyponatremia of water intoxication must be distinguished from that caused by a progressively decreasing glomerular filtration rate of an aging kidney with its inability to excrete a given water load and from the hyponatremia caused by

prolonged diuretic administration. The water intoxication of ectopic or excess ADH secretion is predominant in the elderly who develop pulmonary (e.g. oat-cell carcinoma) or central nervous system (infections/ infiltrations) disorders.

As to the renin-angiotensin-aldosterone cascade, one observes a progressive drop in plasma renin activity after fifty years of age and this applies for basal situations and also during stimulation by orthostatism or salt restriction. Concurrently, plasma aldosterone and urinary tetrahydroaldosterone concentrations drop but generally to a lesser degree. Therefore hypertension with low renin activity has no physio-pathologic significance in the elderly and although diuretics are mandatory in this group, there is a constant risk of perpetrated hyponatremia.

The Thyroid

The chapter on thyroid dysfunction merits special focus when one comes to discuss elderly populations. There is an undeniable if not inevitable drop in thyroid hormone production rate with age. However the metabolic clearance rate of most hormones is concurrently decreased to a proportionate degree (hence the necessity to reduce replacement doses) so that thyroxine levels are maintained in the normal adult range in healthy old people with preserved normocaloric food intake. Tri-iodothyronine levels may be lowered but still within the low normal range. Thyroid stimulating hormone (TSH) levels remain therefore normal. It is the TSH response to thyrotropin releasing hormone (TRH) that is decreased in elderly males. The TRH test (used to assess pituitary reserve of TSH and prolactin) is thus rendered uninterpretable in this category of patients as it cannot discriminate between normal individuals and men suffering of hypopituitarism or hyperthyroidism. In a number of hospitalised or sedentary people who are particularly undernourished and/or systemtically ill, one observes an isolated fall in circulating T3 (the low T3 syndrome) which implies a deficit in desiodination of thyroxine. (See table 1)

SICK EUTHYROID SYNDROME

Findings:
- T4 & Free T4 Index are low
- T3 is Low or Undetectable
- *TSH is usually normal*
- Reverse T3 is either Normal or Elevated)

Mecanisms:
(a) Preferential production of reverse T3 in response to illness & fasting.
(b) Reduced desiodination of reverse T3 to its metabolites.
(c) Reduced desiodination of T4 to T3 peripherally.
(d) Reduced levels of binding proteins including TBG.
(e) Presence of circulating thyroid hormone binding inhibitors.

TABLE 1

Hyperthyroidism

Only 75% of patients have classic signs and symptoms since ophthalmopathy is very infrequently encountered and goitre is rarer than in younger individuals. There is an increased incidence of multi-heteronodular toxic goitre, toxic adenoma and iatrogenic causes characterised by intake of iodine containing medications, 30% of these incidents being amiodarone induced in this age group.

The real danger is to overlook forms of hyperthyroidism which are paucisymptomatic or even frankly atypical in presentation: unexplained heart failure or tachyarrhythmia, recent onset of hallucinatory or manic-depressive psychoses, profound myopathy bordering on to akinesia should all raise questions about masked/apathetic hyperthyroidism.

Hypothyroidism

The symptoms and signs of hypothyroidism are usually overlooked when such complaints as fatigue, memory loss and hypoacuesis are ascribed to ageing without having a Free T4 and TSH measurement. Goitre is rarely seen with hypothyroidism in the elderly except when it is iodide induced through a mechanism described by Wolff and Chaikoff. Thyroxine levels may be depressed in seriously ill and chronically debilitated patients and this is why hypothyroidism should not be diagnosed on the basis of low T4 levels alone. The T3 level may be in the normal range in hypothyroidism but conversely, the low T3 level with normal or elevated Reverse T3 is consistent with the SICK EUTHYROID SYNDROME mani-fested by a host of acute and chronic systemic illnesses (See table 2). Both these tendencies contribute to the unreliability of testing T3 levels in hypothyroidism. Free T3 is always preferable.

THYROID FUNCTION CHANGES IN AGEING

	Healthy	Thyrotoxic.	1°Hypothy.	Sick Euthy.	Amiodarone
TOTAL T4	N	↑	↓	↓	↑↓
FREE T4	N	↑	↓	N	
TOTAL T3	N	↑	↓/N	↓↓	↓
TSH	N	↓	↑	N	↓↑
FREE T4 INDEX	N	↑	↓	↓	↑↓
REVERSE T3	N			↑	
TSH response to TRH	↓ (males)	↓	↑	N/↑	↓↑
Thyroid hormone product rate	↓	↑	↓	N/↓	
Metabolic clearance rate of thyroid hormone	↓	↑	↓	↓	

TABLE 2

The anaemia of hypothyroidism may be multifactorial when associated with pernicious anaemia or iron deficiency anaemia. Finally, autoimmune polyendocrinopathies (such as that described by Schmidt) may associate hypothyroidism with concomittant adrenal cortex insufficiency and diabetes mellitus so that one should exercise great care in thyroid hormone substitution in myxoedematous elderly subjects and all the more so if coronary insufficiency coexists.

Carbohydrate Metabolism

Disordered carbohydrate metabolism is the most frequently encountered problem to such an extent that nearly 50% of elderly people have some degree of glucose intolerance due to diminished peripheral glucose utilisation associated with insulin resistance rather than insufficient insulin pancreatic reserve and secretion. The mechanism involves an intrareceptor defect of phosphorylation of the B chain component of the insulin receptor resulting in secondary down-regulation of the concentration of receptors in the cell membranes of adipocytes, skeletal muscle etc.

Although, theoretically speaking, the therapeutic goal for diabetes mellitus in the aged is the same as that in younger patients, one must learn to tolerate moderate elevations of fasting plasma glucose rather than to persist in over-enthusiastic control, thereby bordering onto hypoglycaemia. Hypoglycaemia is particularly subtle in the elderly due to impairment of cathecolamine responsiveness resulting in diminished compensatory counter-regulatory gluconeogenesis, and absence of the classic autonomic symptoms such that only belated neuroglycopoenic manifestations tend to prevail. This is why chlorpropamide is generally contraindicated in the elderly with its prolonged time of action and hazardous risk of inappropriate antidiuresis.

An increased incidence of hyperosmolar non-ketotic coma is observed in aged diabetic populations typically developing over days to weeks. This constitutes an emergency possibly presenting with focal or generalised seizures associated with the hyperosmolarity induced by the high serum sodium and blood urea nitrogen.

Bone Metabolism

One must make out clearly the distinction between TRABECULAR osteoporosis (Type I) and CORTICAL osteoporosis (Type II). Type I occurs predominantly in women relatively early in the post menopause and generally presents with vertebral collapse in the sixties. Cortical bone is usually preserved. Trans iliac bone biopsy should enable one to appreciate osteoclastic resorption with induced osteoblastic hyperactivity. Osteocalcine is a bone protein used as a biological marker of bone remodelling and turnover. Hormone replacement therapy with topical oestrogen preparations prescribed as from early menopause has proved to go a long way in preventing or retarding this osteoporosis. Type II (senile) osteoporosis occurs later on (70-80 years) and is typically associated with spontaneous or stress fractures principally of the femoral neck. Here trabecular bone is usually conserved and this renders the therapeutic use of sodium fluoride useless in this form of osteoporosis as this acts solely by increasing trabecular bone formation. Here calcium salts and vitamin D3 are indicated prophylactically.

Other Endocrinopathies

Primary hyperparathyroidism is one of the conditions easily overlooked in the elderly because although the symptomatology is similar to that in younger individuals, bone demineralisation, weakness and osteoarticular complaints are preponderant features of senescence. One must strive to differentiate the hypercalcemia from that induced by malignancy and the presence of a circulating Osteoclast Activating Factor.

Ectopic parathyroid hormone secretion and its entrained hypercalcemia has been described with renal cell carcinoma and hepatomas probably attributed to expression of the Human Parathyroid Related Peptide gene by these tumours.

Other rarer ectopic hormone syndromes affecting the elderly suffering of malignancy are the ectopic 'adenocorticotrophic hormone (ACTH)' production of oat-cell carcinoma of the bronchus which usually is heralded by clinical features of hypokalaemia and of hyperglucocorticism.

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LABORATORY FINDINGS IN METABOLIC BONE DISEASE

	Calcium	Phosphate	Alkaline Phosphatase	Parathyroid Hormone.	Osteo Calcine
1° Hyperparathyroidism	↑↓	↓/N	↑/N	↑↑	↑
2° Hyperparathyroidism	↑	↑	↑	↑	↑↑↑
Osteomalacia	↓/N	↓	↑/N	↑	N/↓
Osteoporosis	N	N	N	N/↑	N/↓
Hyperthyroidism	↑	↑	↑/N	↓	↑
Cushing's Syndrome	N/↓	↓	N/↑	↓/↑	↓/↑
Paget Disease	N/↑	N/↑	↑	N	↑

TABLE 3

Continued from page 3

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