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GUEST EDITORIAL

Endocrine Potpourri

Meng-Hee Tan,* MD, FRCP(C), FACP

This issue of the *Journal* is dedicated to endocrinology and metabolism. The contributions are from members of the Division of Endocrinology and Metabolism in the Department of Medicine at Dalhousie University. Major advances in this specialty have occurred during the past decade. To summarize these advances within the pages of this issue would be impossible. So we have elected to briefly review specific problems commonly encountered by primary care physicians in Nova Scotia.

In the first article, Dr. Allan Shlossberg gives an overview of the screening tests for endocrine disorders, covering the simple tests that can be performed by the primary care physician in diagnosing hyperthyroidism and hypothyroidism, Cushing's syndrome and adrenal insufficiency, anterior and posterior pituitary disorders, hyperparathyroidism, and hypoglycemia. The costs of these simple screening tests are listed and when to refer the patient for further investigation by the specialist discussed.

This is followed by a conducted tour through the maze of investigations and management of endocrine hypertension by Dr. Carl Abbott. He provides guidelines on the diagnosis and treatment of mineralocorticoid hypertension, glucocorticoid hypertension, catecholamine-induced hypertension, and renin-angiotensin-induced hypertension.

In this age of recombinant DNA drugs, it is not surprising that many are available for the treatment of endocrine disorders. After showing us a simple approach to searching for treatable forms of growth deficiency in children, Dr. Sonia Salisbury and Susan Baker share their experience in the use of recombinant-DNA growth hormones here in the Maritimes and across the nation.

As our female population ages, menopause will become a more prevalent endocrine problem. Drs. Roger Rittmaster and William Wrixon provide a comprehensive review of this common disorder and discuss the rationale and guidelines for hormonal replacement in the post-menopausal state. The indications for treatment, potential risks of estrogen replacement, balancing the risks and benefits, types of hormonal replacement and the practical aspects of treatment are presented.

Osteoporosis, part of the menopausal state, can be due to other causes. Dr. Sam York discusses this group of metabolic bone disorders covering the etiology, pathogenesis, investigations and management. The use of calcium supplements, hormonal replacement, and other aspects of treatment are reviewed.

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Diabetes mellitus is another common chronic metabolic disorder affecting 5% of the population. During the past decade, many advances in the management of diabetes mellitus have been made. One of the major advances is self-monitoring of blood glucose by the person affected by diabetes. Today, many devices are available for use by our patients. Dr. Sethu Reddy describes the devices that are available for self-monitoring of blood glucose and also discusses devices that are used to deliver insulin — pumps, pens and jet-injectors.

People with chronic diseases must assume an active role in the day-to-day management of their health care. To attain this important goal, they must acquire the knowledge and skills essential for self-care, an integral component of the management of their disease. In the article on "Patient education in the management of diabetes mellitus", I cover the need for patient education, their effect on acute and certain chronic complications of diabetes, their cost-effectiveness, their relationship with patient compliance and their availability in Nova Scotia.

As members of an academic Division of Endocrinology and Metabolism, we are involved in research, the key to new knowledge and the gateway to more effective treatment, with the hope that we can better understand human biology and alleviate human suffering. In the final article entitled "Research in the Division" we outline the current research being done by members of the Division. This includes basic and clinical research. We collaborate with other clinicians and clinician-scientists here in Halifax and elsewhere around the world in our quest for new knowledge.

Finally, I would like to thank the Editor-in-Chief, Dr. J F O'Connor, for inviting us to prepare this issue and, in so doing, giving us the opportunity to make this small contribution to the medical community in Nova Scotia.

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Screening Tests for Endocrine Disorders

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Many patients present with symptoms which suggest an endocrine disorder, but the symptoms are often nonspecific and only a small fraction of these patients prove to have an endocrinopathy. For example, only a few of the patients complaining of fatigue, weight gain and dry skin have hypothyroidism. Similarly, hypertension and glucose intolerance are common in obese patients, but Cushing's syndrome is rare. Furthermore, early stages of endocrine diseases may not be obvious clinically. Therefore, clinicians require simple, reliable and inexpensive tests to screen for endocrine disorders. Such tests are available and it is important for primary care physicians to understand how to use these to avoid unnecessary and costly investigations.

THYROID

The best screening tests of thyroid function are serum free T4 and serum TSH. If free T4 is unavailable, the free thyroxine index (FTI), derived from the total T4 and T3 uptake tests, will usually suffice, although the FTI does not correct as well as the free T4 for abnormalities in thyroid binding proteins. In a patient with mild hyper- or hypothyroidism, the free T4 or FTI may be within the stated normal range, but still be higher or lower than normal for that individual. Thus it is essential that the TSH always be included. An elevation in TSH is the most sensitive indicator of primary hypothyroidism. Clinical and biochemical hypothyroidism without an increase in TSH suggests a diagnosis of secondary hypothyroidism (abnormal pituitary or hypothalamic function).

The new sensitive TSH assays clearly distinguish low from normal values, and therefore the diagnosis of hyperthyroidism is readily confirmed by the finding of a suppressed TSH. An increased free T4 or FTI in association with a normal TSH must be explained on some other basis, such as an abnormality in thyroid binding proteins. (It is necessary to know if your local laboratory is using a sensitive TSH assay).

All laboratories should now be using a free T4 and sensitive TSH assay for assessing thyroid function. These two tests will usually establish whether a patient is euthyroid, hyperthyroid or hypothyroid. Further testing is seldom necessary, except perhaps to determine the etiology of the thyroid disorder. The radioactive iodine uptake test is expensive, inconvenient and unnecessary for the diagnosis of thyroid disease and, for the most part, this test should not be requested by general practitioners. Thyroid radioisotope scans and ultrasound studies are usually reserved for patients with a palpable nodular thyroid gland.

ADRENAL

Primary adrenal insufficiency (Addison's disease) is very unlikely to be present if the morning serum cortisol is greater than 400 nmol/L, though many normal subjects have much lower values. This diagnosis is confirmed by failure to respond to ACTH stimulation (Cortrosyn®, 0.25 mg I.M. or I.V.) with an increase in serum cortisol to greater than 500 nmol/L. The same tests and responses can be applied in screening for hypoadrenalism secondary to hypothalamic-pituitary disease.

An excellent screen for suspected Cushing's syndrome is the overnight dexamethasone suppression test. One milligram of dexamethasone is administered orally at 2300 hours, and the serum cortisol is measured the following morning at 0800 hours. A value less than 140 nmol/L excludes Cushing's syndrome with only rare exceptions. A higher value does not confirm the diagnosis, since false positive results occur in about 5% of cases due to a variety of reasons. In these individuals, further investigation is indicated, usually beginning with a measurement of 24-hour urine cortisol excretion. Tests to determine the etiology, including CT scanning of the pituitary or adrenals, are indicated only after the diagnosis of Cushing's syndrome has been confirmed by biochemical studies. Tests for hyperaldosteronism and pheochromocytoma are discussed in Dr. Abbott's article on Endocrine Hypertension. (see pg. 77).

PITUITARY

Assessment of pituitary function may require an evaluation of each of the pituitary hormones (growth hormone, prolactin, ACTH, TSH, LH, FSH) and target organs (thyroid, adrenals, gonads). Screening tests for the thyroid and adrenals have already been discussed.

Men presenting with impotence, infertility or galactorrhea should be screened for endocrine disease by measuring serum testosterone, LH, FSH and prolactin. Investigations in women presenting with amenorrhea, galactorrhea or infertility should include estradiol, LH, FSH and prolactin. In the presence of low gonadal steroid levels, low or normal LH and FSH indicate secondary hypogonadism, and high values indicate primary testicular or ovarian failure. An elevated serum prolactin warrants further investigation. The causes of hyperprolactinemia include certain drugs, primary hypothyroidism, pituitary tumors and hypothalamic disorders. Prolactin levels greater than 200μg/L are

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almost always due to a prolactin-secreting pituitary tumor. Since prolactin may increase in response to stress and feeding, samples should be obtained in the resting, fasting state.

Posterior pituitary insufficiency (central diabetes insipidus) is suggested by a history of polydipsia and polyuria in the presence of normal renal function and in the absence of glucosuria. Urine concentrating ability can be assessed by measuring the specific gravity in a urine sample obtained after several hours of fluid deprivation. Significant diabetes insipidus is ruled out by a specific gravity over 1.020 or a 24-hour urine volume less than 2.5 litres.

PARATHYROID

Hyper- and hypoparathyroidism are screened for by measuring serum calcium. This should always be measured in conjunction with the serum albumin, and if the latter is abnormal, an appropriate correction should be made. The serum calcium is adjusted 0.25 mM/L for each 10 gm/L correction in albumin. If hypercalcemia is confirmed, serum parathyroid hormone can be measured. An elevation in serum PTH supports a diagnosis of primary hyperparathyroidism, but in the currently available assays, normal values do not exclude this diagnosis.

HYPOGLYCEMIA

Most patients with spontaneous "hypoglycemia" have symptoms which are not due to low blood glucose. A test strip estimate of finger tip capillary blood glucose is inadequate to distinguish normal from low values in these patients. The diagnosis must be confirmed by a laboratory measurement of serum glucose in a sample obtained during an episode of symptoms. A glucose tolerance test is seldom helpful and more often misleading, since many normal subjects will have a dip in the curve to less than 3 mm/L and sometimes to less than 2.5 mm/L without associated symptoms. In the rare patient with confirmed fasting hypoglycemia, measurement of serum insulin in the same sample will usually distinguish insulinoma from other causes of fasting hypoglycemia.

CONCLUSION

Except for thyroid disorders, patients with positive screening tests for endocrine disease will usually require referral or consultation with an internist or endocrinologist. □

The approximate cost of the tests mentioned here are as follows:

Free T4	$12.00	TSH	$17.00
Cortisol	$15.00	Testosterone	$27.00
Estradiol	$29.00	LH	$18.00
FSH	$18.00	Prolactin	$21.00
PTH	$45.00	Insulin	$12.00
Glucose	$ 2.50	Calcium	$ 3.00

FURTHER READING

Endocrinology and Metabolism Clinics of North America, Diagnostic Evaluation of Endocrine Disorders I and II, Vol. 17, Nos. 2 and 3, 1988.

Endocrine Hypertension — Diagnosis and Management

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Endocrine hypertension syndromes are disorders of multiple etiologies with hypertension as the common clinical feature. They show measurable excesses (or deficiences) of a variety of hormones. These hormones usually can produce hypertension in a variety of experimental animal models. In humans, the characteristic of endocrine hypertension is the reversal of hypertension following: a) medical antagonism of the hormone's effects (spironolactone in primary aldosteronism); b) withdrawal of a pharmacologic agent (oral contraceptive or NSAID); c) removal of the source of hormone excess (such as a pheochromocytoma or adrenal adenoma); d) surgical correction of the pathological abnormality (bypass of renal artery stenosis or angioplasty); or e) termination of pregnancy (removal of the placenta in toxemia).

A good case can be made for considering primary (essential) hypertension as an endocrine disorder because many different abnormalities of hormone secretion or metabolism can be found. These are by no means consistent because primary hypertension is a heterogeneous disorder.

Conventional endocrine hypertension syndromes can be divided into three broad groups (see Table I). This review will concentrate on the more common adrenal forms and renin-dependent hypertension.

TABLE I

Adrenal: Conn's syndrome (aldosterone-producing adenoma and idiopathic hyperplasia), Cushing's syndrome (cortisol producing adenoma, carcinoma or hyperplasia), certain rare forms of congenital adrenal hyperplasia, pheochromocytoma (including extra-adrenal tumors in 10% of cases).

Renal: renin-angiotensin-dependent causes (renal artery stenosis or renin-secreting tumor), renal prostaglandin deficiency (NSAID use).

Other: oral contraceptive induced hypertension, toxemia of pregnancy, malignant hypertension of any cause.

ADRENAL HYPERTENSION

1. Mineralocorticoid Hypertension

Mineralocorticoids produce sodium retention and potassium loss through their effects on the renal tubule. This results in increased resistance in arterial vessels, the result of an increased permeability of arterioles and arteries to sodium and an increase in intracellular sodium concentration in the contractile myocytes. Intracellular calcium plays an important role in this increased arterial smooth muscle contractile activity. (Calcium antagonists can lower peripheral resistance and blood pressure in this form of hypertension very effectively.)

Clues to Mineralocorticoid Hypertension

Unprovoked hypokalemia is the most important clue. However, cases may be missed if the patient is: a) on a sodium restricted diet (this minimizes potassium loss); b) pregnancy (high progesterone levels antagonize aldosterone's renal tubular effects); c) on a potassium-sparing diuretic combination (especially with spironolactone), an ACE inhibitor or calcium antagonist; or if d) blood is taken after prolonged venous stasis with muscle "pumping". Diuretic-induced hypokalemia, if extreme or persistent, should be viewed with suspicion, especially when using a potassium-sparing combination. Hypernatremia, hyperchloremia and a metabolic alkalosis may be found.

Symptoms and signs of hypokalemia (muscle weakness, paraesthesiae, polydipsia, polyuria, hyperglycemia) may be absent. Patients with Conn's syndrome (primary aldosterone excess) usually are resistant to the anti-hypertensive effects of ACE inhibitors and beta-blockers but respond to calcium antagonists. Hypertension may be severe and complicated but malignant hypertension is unusual. Hypokalemia may be associated with accelerated and malignant phase of other forms of hypertension.

What to do if Hypokalemia is found

a) discontinue diuretic use for two to three weeks and use an alpha-blocker (prazosin or terazosin). Oral potassium may be necessary.
b) if hypokalemia persists, collect a 24-hour urine for potassium, sodium and creatinine. If potassium is >40 mmol/TV, inappropriate renal loss is suggested and excludes loss from the gut or inadequate intake. Urinary sodium should be >100 mmol/TV to promote renal potassium loss.
c) When renal loss is confirmed, measure plasma renin activity (PRA) in venous blood after four hours of standing.
d) PRA is usually undetectable on an unrestricted sodium intake, after sodium restriction for a week, after an oral dose of furosemide (40 mg) or after a single dose of an ACE inhibitor (Captopril 25 mg orally). If PRA is unresponsive to these stimuli, the next step should be to
e) measure either 24-hour aldosterone excretion on a normal sodium intake or during salt loading.

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Plasma aldosterone supine or standing is an alternative. If hyperaldosteronism is found,

f) a CT scan of the adrenals is indicated. An adenoma may be found (figure 1) or both adrenals may be enlarged, if there is hyperplasia. Renal cysts are commonly seen on CT scanning in Conn's syndrome.

Aldosterone levels may be normal if chronic hypokalemia is severe as potassium depletion limits steroid secretion by the adenoma or hyper plastic zona glomulosa.

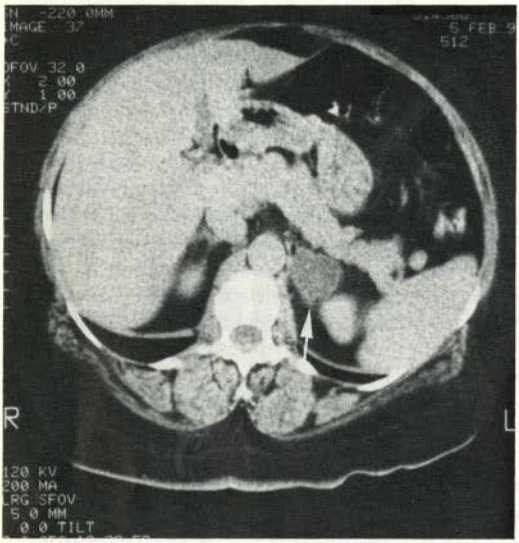

Fig. 1 CT scan of the adrenals in a female with hypertension, long standing hypokalemia, suppressed PRA and high aldosterone levels. There is a large homogeneous mass in the left adrenal (see arrow).

Management

Surgery is usually recommended for adenomas. The expectation is that the hypertension and hypokalemia will remit. Persistent hypertension suggests: a) irreversible functional arteriolar or renal abnormalities (such as nephrosclerosis); or b) associated primary hypertension. A period of spironolactone therapy pre-operatively, with correction of the hypertension and hypokalemia, may predict surgical success. Patients with idiopathic hyperplasia are not cured by bilateral adrenalectomy and should be managed medically with spironolactone, if tolerated (gynecomastia and sexual dysfunction are common in males). Alternatively, a potassium retaining diuretic such as amiloride may be used to correct the hypokalemia and a calcium antagonist or alpha-blocker given for the hypertension.

Congenital adrenal hyperplasia is a rare cause of hypertension and should be suspected if: a) the patient is young; b) hypokalemia and suppressed PRA are found; and c) other features are present (short stature, muscular physique, ambiguous genitalia or amenorrhea in females and hyperpigmentation). Investigation and management is discussed in reference 1.

2. Glucocorticoid Hypertension

Clues to Glucocorticoid (Cortisol) Excess

Other features of Cushing's syndrome may be found: amenorrhea, hirsutism, mood changes, central obesity, muscle wasting, thin skin, striae, osteoporosis, hyperglycemia, etc. Marked hypokalemia occurs more often when mineralocorticoids (deoxycorticosterone, corticosterone) are secreted in large amounts along with cortisol. Cortisol hypersecretion is thought to produce hypertension by: a) sensitizing the arterial contractile cells to circulating catecholamines and angiotensin II (PRA may be increased); b) sodium retention; or c) inhibition of production of renal prostaglandins or prostacyclin. The hypertension may be resistant to the usual drug therapy.

What to do if Glucocorticoid Hypertension is Suspected

a) Do an overnight dexamethasone (DM) test: (1 mg DM at 2300 hours followed by a serum cortisol at 0800 hours the next day). Failure to suppress serum cortisol with DM may occur in an anxious patient, especially shortly after admission to hospital, in depression or in alcoholics. This test can easily be performed outside hospital.

b) Measure urinary free cortisol in a 24-hour urine. If the above screening tests are abnormal,

c) hospital admission is advised or referral to an endocrinologist (or internist with an interest in Endocrinology). The following tests can be performed: plasma ACTH levels, further DM suppression tests over 48 and 96 hours, with low (2 mg/day) and high dose (8 mg/day) schedules. If the patient has Cushing's syndrome, PRA is usually not suppressed, serum DHEAS may be elevated and CT scanning of the adrenals may differentiate hyperplasia (due to an ACTH-secreting pituitary tumor or extra-pituitary neoplasm) and adrenal tumors. In pituitary-dependent cases, a tumor may be visible on CT scanning of the sella tursica.

Ectopic secretion of ACTH from a neoplasm outside the pituitary produces symptomatic hypokalemia but the rapid onset may preclude the development of other classical features of Cushing's syndrome. Hyperpigmentation is an important clue. Adrenal carcinomas commonly secrete androgens and mineralocorticoids in addition to cortisol so that degrees of virilization and hypokalemia can be expected but hyperpigmentation is absent.

Management of Cushing's Syndrome

Adrenal tumors require surgery. The prognosis is excellent with adenomas although contralateral adrenal atrophy may require post-operative steroid replacement. Carcinoma, especially if metastatic, has a very poor prognosis. Pituitary tumors are usually removed if

accessible. Adrenalectomy for hyperplasia is now infrequently performed.

3. Catecholamine-Induced Hypertension

There are several important clues to the presence of a pheochromocytoma: a) associated symptoms of headache, palpitations, attacks of sweating and pallor (not flushing), anxiety and tremulousness; b) hyperglycemia, paroxysmal rises in blood pressure with symptoms, paradoxical elevation of blood pressure in response to a beta-blocker; c) hypertensive episodes during anesthesia or radiologic contrast studies of the kidneys; d) atypical pregnancy-induced hypertension; e) associated hypercalcemia, neurofibromatosis, café au lait skin lesions or thyroid nodule (medullary carcinoma); and f) rarely, if an adrenal mass is palpable.

The hypertension of pheochromocytoma may respond to ACE inhibitors (renin secretion is increased and catecholamine effects are modulated), calcium antagonists or alpha-blockers and the tumor may be unsuspected.

What to do if Pheochromocytoma is Suspected

a) Measure 24 hour urinary free catecholamines, VMA or metanephrines and/or plasma catecholamines, supine and after being upright for several hours. Platelet catecholamines remain high even if plasma levels fall to normal. (Methyldopa will give falsely high urine free catecholamines and certain foods and drinks elevate VMA). If abnormal,
b) admit to hospital.
c) discontinue beta-blocker use and control blood pressure with a calcium antagonist (nifedipine), alpha-blocker or ACE inhibitor. (Hypertensive emergencies in pheochromocytoma respond well to I.V. labetolol).
d) Consider measuring the blood pressure and plasma catecholamine responses to oral clonidine (300/μgm orally), hourly over three hours with the patient supine. Blood pressure frequently falls but catecholamines do not.
e) CT scanning of the adrenals and abdomen.
f) Occult or extra-adrenal pheochromocytomas may be small and detectable only by venous sampling for plasma catecholamines along the inferior or superior vena cava.

Management

Removal is always required. Prognosis is usually excellent with experienced surgeons. Malignant change or behaviour (10% of cases) changes the prognosis and demands long-term surveillance. More details on diagnosis and management of adrenal hypertension can be found in reference 2.

RENIN-ANGIOTENSIN-INDUCED HYPERTENSION

Most cases will have renal artery stenosis with or without complete occlusion on arteriography. Rarely renal tumors may secrete renin and show high PRA levels and hypokalemia due to secondary hyperaldosteronism.

Clinical Clues

a) drug resistant hypertension, especially after a period of good control or early in treatment.
b) a young or elderly hypertensive patient.
c) accelerated or malignant hypertension at any age.
d) a history of renal trauma and hematuria.
e) a systolic-diastolic bruit in the epigastrium or flanks.
f) high PRA levels in a patient with hypokalemia.
g) associated peripheral vascular disease or carotid artery bruit.
h) rapid deterioration in renal function after use of an ACE inhibitor. This is a clue to bilateral renal artery stenosis.

What to do if Renovascular Hypertension is Suspected

Circulating PRA levels are not reliable and they may be influenced by prior treatment regimens. A suggested approach:

a) intravenous digital subtraction angiogram of the renal arteries, is highly sensitive and more so than IVP. In some cases, intra-arterial injection may be preferable, especially if prior radiologic investigations (such as an IVP or nuclear studies) suggest the diagnosis (asymmetry of kidneys or nonfunctioning kidney).
b) nuclear scan or flow study. This is less invasive but is also less sensitive. In some cases, it may be used as a prior screening procedure and is helpful in assessing relative blood flow to each kidney especially if collaterals have developed.
c) measurement of PRA levels in each renal vein and in the lower inferior vena cava. ACE inhibitors should be held for at least two days prior to the test because differences in PRA will be obscured. Oral furosemide (40 mg a day before the procedure) will improve lateralization by exaggerating renin output from the abnormal kidney.

Management

This will depend on outcome of the above investigations. Surgical bypass procedures and nephrectomy are required less often since angioplasty techniques have improved. Angioplasty is much more effective with fibromuscular disease of the renal artery. Some cases may be more appropriately treated with a long-term ACE inhibitor alone or in various combinations. □

References

1. Abbott EC. Adrenal Hyperfunction. *Medicine, North America,* 1987; **13:** 2445-2466.
2. Young WF and Klee GG. (ed.) Diagnostic Evaluation of Endocrine Disorders I, *Endocrinology and Metabolism Clinics of North America.* **17(2),** 1988.

How to Search for Treatable Forms of Growth Deficiency

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The purpose of this paper will be to describe:

a) a classification of short stature based on growth velocity

b) what clinical information should be documented in children with short stature

c) the incidence of growth hormone (GH) deficiency by etiology in the Maritimes and Canada

A CLASSIFICATION OF SHORT STATURE BASED ON GROWTH VELOCITY

The list in Table I is not intended to be all inclusive but to provide a practical way of looking at growth retardation. Hereditary short stature is not generally considered amenable to treatment, though through clinical trials, with long-term follow-up, the judicious use of GH may in the future provide a therapeutic option for some of these children.

TABLE I

SHORT STATURE: A CLASSIFICATION ACCORDING TO GROWTH VELOCITY

Normal Growth Velocity

- Hereditary short stature
  - normal child
  - intrauterine growth retardation
  - miscellaneous dysmorphic syndromes
  - bone and cartilage defects

  chronological age = bone age > height age
- Constitutional short stature

  chronological age > bone age and height age

Decreased Growth Velocity

- Endocrine disorders
  - hypothyroidism
  - glucocorticoid excess
  - growth hormone deficiency
  - Turner's Syndrome*
  - Rickets (hypophosphatemic/VIT—D dependent)
- Secondary to systemic illness
- Malnutrition/deprivation

  chronological age > bone age and height age

*Bone age is usually normal in prepubertal years

Constitutional short stature is a term used for a group of children, usually boys, who fall below the 3rd percentile in the first 2 years of life, then grow below but parallel until puberty, which is often delayed. There is generally a family history in father or grandfather, and a good prognosis for normal adult height.

Those children with decreased growth velocity represent the group that require detailed investigation. We have placed Turner's syndrome under endocrine disorders because of its endocrine manifestations. The growth velocity in this condition decreases continuously throughout the prepubertal years, though the bone age may be normal. GH treatment may improve final adult stature, and a Canadian clinical trial is underway to study effectiveness and safety.

WHAT CLINICAL INFORMATION SHOULD BE DOCUMENTED IN CHILDREN WITH SHORT STATURE?

A clinical check list (Table II) should routinely be carried out in all children with a presenting complaint of short stature. In some cases, remeasuring carefully (Table III) every 3 months with calculation of the growth velocity (Table IV) and an x-ray of hand and wrist to document the bone age, may be all that is needed. Children grow seasonally, making any calculation of growth velocity inaccurate unless 6 months to a year have elapsed.

TABLE II

CLINICAL CHECK LIST
CRITICAL THINGS TO ASK AND DO

- **General information**
  - —birth history — pre, intra, postpartum
  - —family history, including heights and pubertal development
  - —past or chronic illnesses
  - —medication history
  - —eating habits
- **Growth history**
  - —age of onset of growth failure
  - —past heights and weights
- **Physical examination**
  - —accurate height to nearest millimetre
  - —weight
  - —body proportions/pubertal stage
  - —? congenital anomalies

Boys with constitutional pubertal delay grow very slowly (often < 4 cm/year) in the period immediately before significant testicular enlargement begins to occur. These children need to be followed at 3-monthly

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intervals to be sure that there is no important cause of true growth retardation.

TABLE III

MEASUREMENT TECHNIQUES

1. Shoes and socks off
2. Jeans off
3. Back to the wall; steel tape on wall
4. Heels together, shoulders loose, knees straight, back touching wall
5. Hold head, with your hand giving gentle pressure under angle of mandible to keep head straight, child's eyes straight ahead
6. Object to make a right angle with wall and child's head
7. Do at least 3 measurements to nearest millimetre

TABLE IV

GROWTH VELOCITY

Age (years)	Rate (cm/year)
2 — 4	7 — 8
5 — prepubertal	5 — 6
Pubertal	Variable

Abnormal < 4 cm/year AT ANY AGE

Where greater concern exists on historical or physical grounds, then the tests outlined in Table V, separated into screening or more specific tests, should be performed. Patients with hypothyroidism may have growth failure as their only complaint, and all girls with short stature, even in the absence of classic features of Turner's syndrome, deserve a chromosome analysis. Clinical judgement must be exercised in obtaining appropriate laboratory tests.

TABLE V

LABORATORY EVALUATION OF THE SHORT CHILD

Screening Tests

- CBC ± Sed rate
- urine analysis
- creatinine
- capillary blood gases
- electrolytes
- TSH
- chromosome analysis (girls)
- bone age

Specific Tests

- CT scan
- GH testing — provocative
  — physiological
- tests to rule out causes of growth failure secondary to chronic disease, e.g. Crohn's disease, rickets

Measurement of a single random GH level is rarely helpful because unless the GH level is 8 μg/L or more, it does not distinguish normal from abnormal. A useful office screen is to have the child, who has had no food or carbohydrate of any kind for at least 2 hours, run rapidly up and down stairs for about 20 minutes before drawing a blood sample 20 minutes later. Even then, between 10% and 20% of normal children may not reach an adequate peak, but a value above 8μg/L can be reassuring.

WHO HAS RECEIVED TREATMENT?

Eighty children in the Maritimes have received GH treatment since 1966, an incidence of GH deficiency of 1.6 per 100,000 children per year under the age of 15. At any given time, about 35 children are receiving GH because treatment is continued until growth is considered either adequate or complete.

Table VI illustrates the distribution of patients by etiology in the Maritimes and nationally. The preponderance of cases remain idiopathic with GH deficiency being secondary to hypothalamic dysfunction. This group includes children with the appearance of classic GH deficiency (Figure 1), but also others with less well defined physical characteristics.

TABLE VI

ETIOLOGY OF GROWTH HORMONE DEFICIENCY IN PATIENTS TREATED WITH GROWTH HORMONE 1966-1989

Diagnosis	Maritime Cases	% Total	National Cases	% Total
Idiopathic	35	(43.75)	770	(61.8)
Space occupying lesion, hypothalamic-pituitary region	19	(23.75)	212	(17.0)
Postcranial radiation	12	(15.0)	166	(13.3)
Congenital midline defects	7	(8.75)	44	(3.5)
Familial	6	(7.5)	39	(3.1)
Trauma	1	(1.25)	16	(1.3)
TOTAL	80		1247	

The next most common cause of GH deficiency is secondary to space-occupying lesions, most commonly craniopharyngioma in childhood. Growth retardation that appears suddenly without any other symptoms may be a helpful diagnostic clue, as illustrated in Figure 2.

Cranial radiation may result in GH deficiency which is partly dose dependent. The deficiency may be partial and not all children will require treatment.

Optic nerve hypoplasia is the most common midline defect resulting in GH deficiency, and all such children are carefully screened in the preschool years.

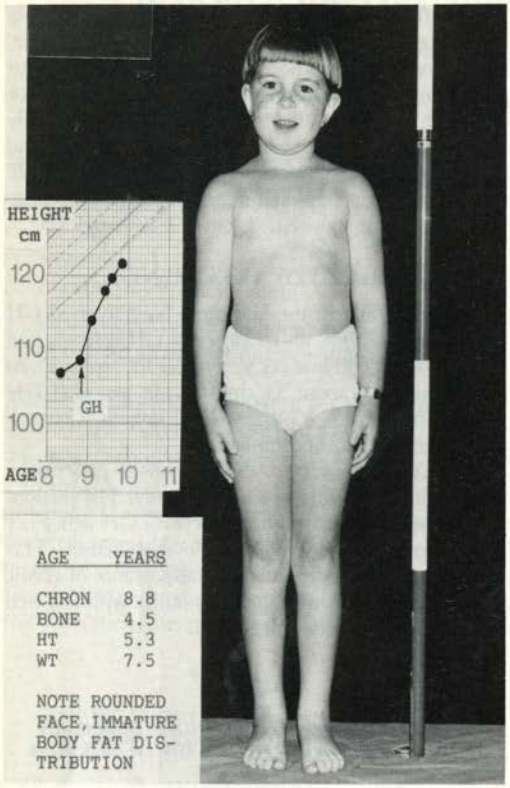

Fig. 1 Classic features of isolated hormone deficiency.

In Canada, since 1966, the Canadian Growth Hormone Advisory Committee, with representation from all pediatric endocrinology specialty centres, has monitored the safety and efficacy of GH treatment and has defined the Canadian criteria for the diagnosis of GH deficiency. These criteria are based on growth velocity and GH levels following physiological and provocative testing. With the advent in 1985 of recombinant DNA GH, the need for evaluation of the use of GH under controlled conditions remains the mandate of this committee. The

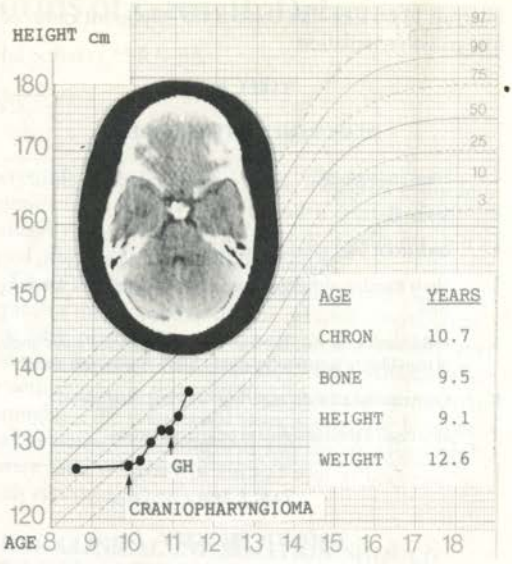

Fig. 2 Growth retardation due to craniopharyngioma. Post-operative improvement in growth secondary to marked hyperphagia. At age 11, growth hormone treatment required.

ready availability of recombinant DNA GH has provided a possible therapeutic modality for children other than those with profound GH deficiency. To predict which child will have a height which will fall unacceptably below the normal range and who might safely benefit from treatment, would seem to be our responsibility in the next decade. □

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Post-Menopausal Hormone Replacement

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Post-menopausal hormone replacement is a relatively recent phenomenon. Beginning in the mid 1960s estrogens were prescribed with increasing frequency to post-menopausal women to relieve symptoms of estrogen deficiency. In the mid 1970s, after the discovery that women who received estrogens alone (unopposed by progestins) had an increased risk of developing endometrial cancer, physicians became increasingly reluctant to recommend hormone replacement, and women themselves were less likely to continue long-term estrogen therapy. More recently, as the potential benefits of post-menopausal hormone replacement have become apparent and newer treatment protocols have reduced the incidence of uterine bleeding, this therapy is again becoming widespread. Nevertheless, concerns about long-term safety have caused lingering doubts in both physicians and patients. This review will address the issues of post-menopausal estrogen, progestin, and androgen replacement.

INDICATIONS FOR HORMONE REPLACEMENT

Menopausal symptoms

Vasomotor flushes (hot flashes) are a symptom of estrogen withdrawal, while vaginal dryness and itching, dyspareunia, and dysuria may be symptoms of estrogen deficiency. This is more than a semantic difference, since hot flashes will generally improve with time, while symptoms of vaginal atrophy may become worse. Psychological symptoms such as depression and anxiety also are common during the perimenopausal years, but the relationship of these symptoms to changes in hormonal status is unclear.

Hot flashes and symptoms of vaginal atrophy all respond well to estrogen replacement in most women. Psychological symptoms in some women may be related to hot flashes and vaginal atrophy, and in these women estrogen replacement may be helpful. However, such psychological symptoms commonly respond to placebo treatment as well, and they are not an indication for long-term hormone replacement.

Loss of libido

Decreased libido may occur in both older men and women. In women, the relationship of libido to hormonal factors is far from clear and, whether androgens, estrogens, or both play a dominant role is unknown. While estrogen production ceases in the post-menopausal ovary, androgens continue to be secreted. Adrenal androgen production declines with age, but this should not be a factor in women with intact ovaries. Certainly, hormonal replacement is indicated in women who have decreased libido secondary to discomfort from vaginal atrophy. Estrogen or androgen replacement is not indicated in the premenopausal woman. Many physicians empirically use estrogen and/or androgen replacement to treat loss of libido in older women, and some patients will respond. Unfortunately, a well-designed, placebo-controlled trial has not been published on this subject.

Osteoporosis

Bone mass reaches a peak around age 30 and gradually decreases thereafter. Hypogonadism in both men and women is associated with decreased bone mass, and the rate of bone mineral loss increases temporarily at the time of menopause. Estrogens increase intestinal calcium absorption and may decrease the sensitivity of bone to parathyroid hormone. If estrogens are given in the perimenopausal period, the increased rate of bone loss can be prevented and a temporary increase in bone mineral density may be seen. Estrogens may also retard bone loss later in the menopausal years, but estrogens will not reverse established osteoporosis. A reduced incidence of osteoporosis-related fractures has been demonstrated with estrogen treatment. While calcium supplementation alone cannot prevent post-menopausal bone loss, women at risk for osteoporosis should consume 1000 to 1500 mg elemental calcium daily, which generally means a daily dietary supplement of 500 to 1000 mg elemental calcium (e.g., two Tums® twice daily).

The question often arises as to which perimenopausal patients are at increased risk for osteoporosis and how should they be followed. Risk factors include caucasian race, thin body habitus, family history of osteoporosis and/or longevity, immobilization, and possibly smoking, lack of exercise, and low calcium diet. Endocrine disorders associated with osteoporosis include hypogonadism (in both men and women), hyperthyroidism, hyperparathyroidism, and Cushing's syndrome (excess cortisol). Dual-photon bone densitometry is available at the Camp Hill Hospital in Halifax and can be used to screen patients. Women in the upper quartile of bone density are at a low risk of osteoporosis, while women in the lower quartile are at increased risk. Beyond this, bone density is not a good predictor of fracture risk in an individual patient. Furthermore, the technique is insufficiently precise to be used as a means of following individual patients over the short term.

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Coronary Artery Disease

Compared with men, women have increased high density lipoprotein and decreased low density lipoprotein concentrations in their serum, which is associated with a decreased risk of coronary artery disease. This more favorable lipid profile tends to disappear after menopause and can be restored by estrogen replacement. While one might anticipate a beneficial effect of estrogen replacement on the incidence of coronary artery disease, the epidemiologic data are conflicting. Recent reviews concerning the effects of postmenopausal estrogens on the risk of atherosclerosis have come to different conclusions. While estrogens are unlikely to increase the risk of coronary artery disease, a strong protective effect has yet to be proven.

POTENTIAL RISKS OF ESTROGEN REPLACEMENT

Side effects

Estrogens can cause headaches, mood changes, breast tenderness and nausea. These side-effects are generally dose-related. While estrogens generally cause a slight reduction or no change in blood pressure, an occasional woman demonstrates a marked increase in blood pressure with oral estrogens. Similarly, oral estrogens can cause venous thrombosis in women pre-disposed to this problem. No increased incidence of venous thrombosis has been found with post-menopausal estrogen replacement in women who had no prior history of venous thrombosis. Hypertension and venous thrombosis are also not a problem with transdermal estrogens (Estraderm®) or estrogen vaginal creams. Estraderm can, however, cause skin irritation, necessitating frequent rotation of the patch or discontinuation of transdermal therapy.

Endometrial Cancer

Estrogens, when unopposed by progestins, can cause endometrial hyperplasia, which can lead to endometrial cancer. The association between post-menopausal estrogen use and endometrial cancer has been confirmed in numerous studies. Unopposed estrogens confer a 2 to 4 fold increased risk of endometrial cancer, from about 1 case per 1000 women per year to as much as 4 cases per 1000 women per year of estrogen use. The use of cyclic estrogens alone does not prevent this increased risk.

Cyclic progestins when added to estrogens can prevent endometrial hyperplasia and should be protective against endometrial cancer. Unfortunately, regardless of how cyclic progestins are given, they are associated with menstrual bleeding. This has led to the concept that continuous estrogen/progestin therapy may both protect against endometrial cancer and induce endometrial atrophy (and amenorrhea). Such combined, continuous therapy may cause menstrual spotting during the first several months of use in perimenopausal women, but amenorrhea is the rule thereafter. Because of the relative novelty of this approach, most gynecologists recommend periodic endometrial sampling until endometrial atrophy is confirmed.

Breast Cancer

Estrogens are contra-indicated in women with a history of breast cancer, and prolonged estrogen exposure (early menarche, late menopause) has been associated with a higher incidence of breast cancer. This knowledge has led to the concern that post-menopausal estrogen use may lead to an increased incidence of breast cancer. Numerous studies to date have addressed this issue and have produced varying results. Taken together there is no significantly increased risk of breast cancer in women who have received estrogens as a group, there is no consistently increased risk in any subgroup (including those at high risk of developing breast cancer), and there is no consistently increased incidence of breast cancer as a function of dose or duration of estrogen therapy. On the other hand, breast cancer is common, and even a 1% increased incidence of breast cancer in estrogen users would have a major impact on a population basis. There is also the possibility that estrogen therapy may lead to the earlier appearance of a pre-clinical breast cancer. The relevance of these data for the individual patient is currently difficult to assess. Cyclic progestins have been hypothesized to reduce the incidence of breast cancer, but the early data on which this theory was based were inadequate, and one recent study does not support this hypothesis.

Other risks

Post-menopausal oral estrogens may be associated with up to a 2.5-fold increased incidence of gallstones. Post-menopausal estrogens neither increase the risk of ovarian cancer nor worsen glucose tolerance.

BALANCING RISKS AND BENEFITS

On a population basis, the anticipated reduced mortality from a reduction in hip fractures in women receiving estrogens would far outweigh any possible increased mortality associated with breast or endometrial cancer. For the individual patient and physician, however, the decision must rest on incomplete data and may involve concerns or fears that have little to do with experimental evidence.

The benefits of estrogen replacement in a woman at high risk for osteoporosis and low risk for breast cancer are clear. If she had a hysterectomy, estrogens can be given on a continuous basis without progestins. In a woman who has a family history of breast cancer, regular mammograms are indicated, whether or not one is contemplating estrogen replacement. Estrogens are contraindicated in women with a personal history of breast or endometrial cancer. While liver or thromboembolic disease are contraindications for oral estrogens, they are not absolute contraindications for transdermal estrogens. The presence of hypertension, coronary artery disease, or diabetes are not contraindications to estrogen use. In women who have not had a hysterectomy,

progestins should be given to prevent endometrial hyperplasia (see below).

TYPES OF HORMONE REPLACEMENT

Estrogens

Estrogen preparations include: 1) estradiol, the most potent human estrogen; 2) conjugated equine estrogens (Premarin®); and 3) synthetic estrogens (ethinyl estradiol, mestranol). While the estrogen preparations differ in their bioavailability and pharmacokinetics, they all exert their activity through the estrogen receptor and cause similar effects on target organs. The mode of administration, however, has a substantial impact on potential benefits and side-effects. Oral estrogens reach the liver in high concentrations, resulting in an increased production of renin substrate (which can cause hypertension in susceptible individuals) and clotting factors (which can cause thrombosis in predisposed individuals). Hepatic effects of estrogens are also responsible for the changes in serum lipids, which may reduce the risk of coronary artery disease. Parenteral estrogen replacement, including transdermal estrogens (Estraderm®), should have minimal or no hepatic effects, when given in replacement doses. Beneficial effects on bone density should be achievable with any estrogen formulation.

Progestins

Progestins are given to prevent endometrial hyperplasia, which occurs when estrogens alone are used. They are unnecessary in women who have had a hysterectomy. Two synthetic progestins, medroxyprogesterone acetate (Provera®) and norethindrone (Micronor®) are available in Canada as single agents. Both are generally given orally, although medroxyprogesterone acetate can also be given in a long-acting intramuscular preparation (Depo-Provera®). Both preparations can have the opposite effect on serum lipids as do estrogens, but these effects are minor when progestins are given in low doses. Side effects of progestin administration may include abdominal bloating, weight gain, breast tenderness, headaches, and mood changes (the same symptoms which can occur with the premenstrual syndrome).

Androgens

The role of androgens in post-menopausal hormone replacement is controversial. Unfortunately, they are often misused. The average premenopausal woman makes about 7 mg testosterone monthly. This production gradually decreases in post-menopausal women, but remains substantial in women with intact ovaries. One millilitre of injectable testosterone and estradiol in oil (Climacteron®) contains 69 mg testosterone, or about 10 times as much testosterone as the average *pre*menopausal woman makes. No wonder side effects of hirsutism, baldness, and deepening of the voice are seen in women receiving this medication! Testosterone enanthate (Delatestryl®), which contains 140 mg testosterone per millilitre, may also be given as a monthly intramuscular injection, as long as appropriate doses are used. Methyltestosterone (Premarin with Methyltestosterone®), an oral testosterone preparation, is erratically absorbed and appropriate replacement doses are difficult to assess.

PRACTICAL ASPECTS OF HORMONE REPLACEMENT

Before initiating hormone replacement, the benefits and risks of this therapy should be discussed with the patient. Pharmaceutical companies involved in post-menopausal hormone replacement often have educational monographs for patients, and it is worthwhile to keep a supply of these in the office. A history and physical examination, including breast and pelvic exam, should be done to assess the risk of estrogen-dependent neoplasia. Blood pressure should be monitored before and during treatment. A mammogram should be done prior to treatment to search for pre-clinical breast cancer. An endometrial biopsy should be performed if there is a history of abnormal vaginal bleeding suggesting endometrial hyperplasia or neoplasia.

Occasionally, perimenopausal women will present with amenorrhea, but no evidence of estrogen deficiency. Often these women are obese, and they may be converting adrenal steroids to estrogens in their adipose tissue. We recommend giving such women a seven day trial of 10 mg medroxyprogesterone acetate (Provera®) daily. A subsequent withdrawal bleed confirms the presence of continued estrogen stimulation of the endometrium. Since these women are not ovulating or producing progesterone, they are at risk of developing endometrial hyperplasia. Consideration should be given to doing an endometrial biopsy to rule out hyperplasia. If the biopsy is normal, Provera® should be given periodically (every 3 to 6 months) until withdrawal bleeding no longer occurs. At that point hormonal replacement can be given, if indicated.

In postmenopausal women who have had a hysterectomy, continuous estrogen therapy, is appropriate. To relieve symptoms of estrogen deficiency 0.625 to 1.25 mg daily of conjugated equine estrogens (Premarin®) or 50 to 100μg transdermal estradiol (Estraderm®), changed twice weekly, should be adequate. The lowest dose that relieves symptoms should be used. For vaginal atrophy, estrogenic vaginal creams may be used. The dose to treat local symptoms is about one-fourth of the oral dose; however, vaginal estrogens are well-absorbed and can also be used for systemic therapy. For prevention of osteoporosis, 0.625 mg conjugated estrogens or the equivalent should be used.

In women with a uterus, estrogens can and should still be given continuously. Cyclic estrogens do not reduce the incidence of endometrial hyperplasia, may be less effective in preventing bone loss, and may be associated with symptoms of estrogen deficiency during the off week. A progestin should be given in such women to prevent endometrial hyperplasia. This can be

prescribed cyclically, such as medroxyprogesterone acetate, 5-10 mg daily, or norethindrone, 1 mg daily, for the last 12 days of each monthly cycle. Monthly menstrual bleeding can be expected with cyclic therapy.

Alternatively, continuous progestins (2.5 mg medroxyprogesterone acetate or 0.35 mg norethindrone daily) can be given. Continuous progestin therapy may be associated with irregular vaginal spotting during the first 3-6 months of use, especially in peri-menopausal women, but generally amenorrhea and endometrial atrophy are present after 6 months of use. Until more information is obtained regarding such continuous therapy, endometrial biopsy is recommended after 6 months to confirm endometrial atrophy.

In women complaining of decreased libido, a psychosexual history should be obtained, as psychological problems are common during the perimenopausal years. Sexual and/or marital counseling should be considered when indicated. A trial of estrogen or androgen replacement may also be warranted, although this is controversial. Testosterone enanthate (Delatestryl®), 0.05 ml (7 mg) i.m. monthly, is a suitable choice for androgen replacement. With this low dose, side effects such as hirsutism or baldness should be uncommon.

SUMMARY

Post-menopausal hormone replacement will remain controversial until long-term prospective data become available to balance the risks and benefits of such therapy. Some authors, emphasizing the reduction in osteoporosis-related morbidity and mortality and probable reduction in cardiovascular deaths, insist that nearly all women should receive estrogens in the menopause. Other investigators, pointing to the uncertainty surrounding the relationship of breast cancer to long-term estrogen replacement, believe that treatment should be individualized, and the relative benefits and risks carefully discussed with each patient. From an epidemiological perspective, the benefits of estrogens may well outweigh the risks. On an individual basis, however, risk factors for osteoporosis, cardiovascular disease, and breast cancer can be assessed, allowing the physician to recommend estrogens for those women most likely to benefit from them. □

FURTHER READING

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Osteoporosis: Management and Treatment

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Osteoporosis refers to a group of metabolic bone disorders characterized by a reduction in the mass of bone per unit of volume, which is less than that required for adequate mechanical support. The bone is normal in composition but there is not enough of it. Throughout life, bones undergo resorption and formation resulting in replacement of old bone with new bone. The balance of the two processes reaches its peak around the age of 30 to 40. After that age, the rate of resorption exceeds the rate of formation and the bone mass progressively declines in both sexes.

Any condition which causes the rate of bone loss to accelerate eventually results in inadequate bone for skeletal support and fractures occur. Not only does the bone mass decrease with age, but older people are often unstable on their feet and many medications interfere with balance. The result is that falls are more common in older people, and their bones are more fragile. The resulting morbidity and mortality of bone fractures in the elderly is an important problem.

ETIOLOGY

When considering the cause of osteoporosis, one must determine whether it is generalized or localized. Conditions such as rheumatoid arthritis can cause localized thinning, and should be ruled out. If generalized, the condition may be secondary to such conditions as hyperthyroidism, hyperparathydroidism, Cushing's syndrome, and diffuse malignancy such as multiple myeloma.

Once these conditions are ruled out, two types of primary osteoporosis have been described. Type I osteoporosis ("postmenopausal osteoporosis") is characterized by crush injuries of the mid-thoracic to lumbar vertebrae, often occurring with minimal or no injury. Colles' fractures of the wrist are also common. Both fractures involve trabecular bone. Most patients are women but it can affect men as well, so that the preferred term is "Type I". The second form, Type II ("senile osteoporosis"), is characterized by a high frequency of hip fractures. Unlike Type I, where the ratio is about 6:1 female to male, that for Type II is only 2:1. These individuals also tend to be older (> 70 years of age). Fractures of pelvis, proximal tibia, proximal humerus as well as wedge fractures of vertebrae, occur.

PATHOGENESIS

Extensive investigations of the pathogenesis of primary osteoporosis have revealed several important factors, which are valuable for preventing and treating the condition. These include hormonal status such as the loss of estrogen (and testosterone in men). Hyperprolactinemia and exercise-induced amenorrhea with associated suppression of estrogen levels are two examples of hormone loss, in addition to the menopause in women or castration in men.

Genetic factors such as body size, race and adiposity, are important. Individuals with small bone size and who are Caucasian or Oriental, are at greater risk than those at large bone size or who are Black. (Hispanics tend to be intermediate between Caucasians and Blacks). Obese people have a lower frequency of osteoporosis than do lean people. Exercise, provided it does not lead to amenorrhea, decreases the risk of osteporosis. A diet high in calcium throughout life is another important preventive factor. A weak association exists between smoking, excessive alcohol and coffee, and the presence of osteoporosis.

DIAGNOSIS

Diagnosis usually requires special investigations since the patient with osteoporosis shows no abnormalities of serum calcium, inorganic phosphorus and alkaline phosphatase, the markers of metabolic bone disease. (When these abnormalities are found, other types of bone dysfunction or secondary causes of osteoporosis should be looked for).

Routine bone X-rays are not sensitive enough for detecting the presence of early osteoporosis. Approximately 30 to 50% of bone density may disappear before being detected by visual interpretation of bone X-rays. Instruments which measure bone density accurately are now available. Single beam densitometry measures the density of forearms, which are predominantly cortical bone. Dual beam instruments can measure the density of vertebrae and the femoral neck (trabecular and cortical bone, respectively). Other methods of measuring bone density include computerized tomography, which is very specific but not as sensitive as dual beam densitometry.

It should be noted that while we are able to measure bone density more accurately, there is still uncertainty about the practicality of using it as a screening tool, mainly because assessment of bone density does not predict accurately those patients who are at risk of bone fracture.

MANAGEMENT

Management consists mainly of prevention. Patients with advanced osteoporosis are difficult to treat and to date, no method will reverse the process completely. The best that can be expected is a slight increase in bone

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density but frequently, only prevention of further loss is all that can be achieved or a slowing of the rate of loss.

One of the most effective methods of prevention consists of replacement estrogens in women who have entered the menopause. (Men who are hypogonadal should receive testosterone, using depot forms of injectable testosterone). The benefits of estrogens in women must be weighed against the risks. These include hypertension, thromboembolism, gall bladder disease and endometrial carcinoma. Increased risk of breast disease should be considered but the risk of carcinoma seems to be very low. The risk of endometrial carcinoma in those who have a uterus can be decreased markedly by adding a progestin, which ensures periodic shedding of the endometrium. However, this leads to the often undesirable return of menses.

The usual recommendation is conjugated estrogens. Premarin® 0.625 mg daily for the first 21 days of each month, and medroxyprogesterone acetate, Provera® 10.0 mg daily from days 12 to 21. The patients should also have periodic gynecological examinations.

Increased dietary calcium should be encouraged as long as there is no risk of kidney stones. The equivalent of 1500 mg daily as skimmed milk or supplements, is recommended. The patient should take at least 400 I.U. of vitamin D. Larger doses have not proven to be effective, and may lead to hypercalemia or kidney stones.

Patients should remain active. Exercise has been shown to increase bone mass but a very vigorous program is required, and it must be supervised in order to encourage continued participation. As noted above, it would seem prudent to advise patients to stop smoking, and to consume only moderate amounts of caffeine and alcohol.

Treatment of established and symptomatic osteoporosis consists of the management of pain during the phase of bone fracture, early ambulation and exercise. Back braces are generally avoided but some find that they give a degree of comfort. Patients must be taught to learn to live with their backs, and to avoid forward flexion. Special care must be taken to prevent falls or jarring movements. Medications which cause unsteadiness should be avoided. Estrogen replacement in postmenopausal women (with added progestin in those with a uterus) in the same doses used in prevention, is recommended provided the risks are considered. The effectiveness of using estrogens ten or twenty years after the menopause is uncertain. Calcium supplements should be given but alone are not effective in reversing osteoporosis. Estrogens can provide slight increase in bone density and decrease the rate of fractures. Vigorous exercise is usually not practical.

A number of other forms of treatment for osteoporosis are currently under investigation. The effectiveness of fluoride therapy has been reported in which increased bone formation occurs with doses of 40 to 80 mg per day. However, a significant number of patients develop gastric distress or painful arthropathy and must discontinue the medication. For the time being, this drug should be considered only as an investigative drug. Other studies, using calcitonin or parathyroid hormone, have been carried out with some success. Androgens have been used with limited success but the masculinizing effects in women are usually unacceptable. □

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RESEARCH IN THE DIVISION

Continued from page 97.

developed quantitative, precise and specific immunoassays to measure urinary human chorionic gonadotrophin (hCG), serum and salivary carcinoembryonic antigen (CEA) levels in normal women and in those with benign breast disease or breast cancer. They have observed statistically significant elevated levels of these tumour markers in some women with benign breast disease or cancer.

The long term management of children with isosexual precocious puberty using LHRH agonist therapy (Buserelin, Hoechest; Lupron®, Abbott) is ongoing since 1984. Of special interest to Dr. Salisbury in this study is the final height achieved as compared to predicted height.

As a member of the Committee to Study Adverse Effects of Environment on Health, Dr. Abbott is studying the causes and effects of presumed environmental hypersensitivity. His group will try to answer the question: can diagnostic criteria be defined for this illness? Are there differential environmental exposures in those with this illness compared to controls?

CONCLUSION

Though few in number and limited in resources, the Division of Endocrinology and Metabolism at Dalhousie University firmly believes in and is committed to the search for new knowledge through research that will lead to better understanding of human biology and better ways of alleviating human suffering. □

Devices and Diabetes Mellitus

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Diabetes mellitus, perhaps more than any other medical condition, has entered the world of technology with some success and great hope. The problem that the patient and physician face is 'how can we achieve euglycemia?'. It seems simple enough but it actually is not one problem but a series of many complex issues.

In this brief review, the impact of technology in diabetes management will be detailed, with particular focus on self- monitoring of blood glucose and on improved insulin delivery systems. Also, the use of computers will be examined and future expectations from this marriage of available technology with the needs of the diabetic patient will be outlined.

Monitoring of glucose levels has undergone a vast change in the last ten years. From relying on inaccurate urine glucose estimations, we have progressed to being able to determine the actual blood glucose level conveniently at any time. Self-monitoring of blood glucose (SMBG) is now widely accepted as a crucial component of diabetes education and management. It is estimated that 50% of Type I diabetics and about 12% of Type II diabetics currently monitor their blood glucose levels. Both short-term and long-term adjustments of insulin dosage as well as prevention of potential emergencies are possible with accurate SMBG.

Self-Monitoring of blood glucose is ... a crucial component of diabetes education and management.

However, as one would expect, the benefits of SMBG cannot be obtained by simply prescribing the reagent strips and asking the patient to keep a record of his/her blood sugars. There are many factors which affect the reliability of the blood glucose results. The patient's social background, attitudes about their own ability to estimate their blood glucose subjectively, and fears of hypoglycemia are but a few of the variables. Most patients can be instructed to perform SMBG adequately and can make the correct adjustment in their therapy if properly trained and if well motivated.

Even after receiving the proper training, some recent reports suggest that the records kept by patients are often unreliable, due to fabrication, omission or alteration of test results. Thus it is very important to encourage the patients and to advise them of the importance of reliable book-keeping. A few accurate results are more useful than a multitude of untrue numbers. When using this technique for in-patients of hospitals, it is essential that nurses regularly participate in a quality control program.

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For example, patients requiring twice daily insulin injections, would adjust their A.M. fast-acting insulin based on the 1100 glucose, their A.M. intermediate-acting insulin based on 1600 glucose, their P.M. (pre-supper) fast-acting insulin based on the 2200 glucose and their P.M. intermediate-acting insulin based on the fasting 0700 glucose. However, the physician should not blindly ask the patient to perpetually perform SMBG four times a day. Initially or after major changes in management, this may be necessary; but once the patient is stable, the monitoring may be performed once or twice a day at different times of the day (preferably before meals). Generally, insulin-requiring diabetics need to monitor more frequently.

It is always important to ask ourselves, "How are we (patient and physician) making use of the SMBG data?" If the patient does not have the necessary knowledge of diabetes to make adjustments in his regimen and/or if the physician sees the patient at infrequent intervals, the SMBG data is being wasted!

Currently, SMBG may be performed by visually estimating the change in color of the reagent strips. The strips are impregnated with the enzyme glucose oxidase and the reaction of glucose with this enzyme is paired with a change in color of the paper on the strip. There are also reflectance meters which can determine the color changes more accurately and display the glucose concentration. Unlike the initial meters, the current models do not require one to wipe or wash the reagent strip but only to blot the strip dry before inserting it into the meter. Medisense, in its Exactech system, uses a biosensor which detects electrochemical changes in the strip. Over the last ten years, the marketplace has become a large showroom full of many styles of reflectance meters. They are all fairly simple to use and are of acceptable accuracy. It is often the patient's or physician's own personal tastes which dictate the model purchased.

The patient must be comfortable with the visual system prior to committing oneself to the use of a meter.

Some points to keep in mind when deciding are:

1) portability of the meter,
2) ease of use,
3) expense,
4) availability of accessories,
5) quality of technical support and
6) insurance coverage.

The meters currently are almost one-third of the cost ten years ago and many manufacturers offer rebates or trade-in values. One may obtain a price list of the various meters from the Nova Scotia Branch of the

Canadian Diabetes Association (1221 Barrington Street, Halifax, NS, B3J 1Y2). Of course, all meters need to be cleaned and calibrated regularly. Occasional comparison of patient's results with those of the hospital laboratory is also important.

Although the technology of actually estimating the blood glucose has changed little, the packaging and added features have progressed greatly. Meters which are the size of a credit card or a pen are available. Some have been adapted to give audible reports for the visually impaired. Others have memory recall for up to 30 glucose values while others store the data for later retrieval by the appropriate computers. Thus, the data need not only be recorded in a diary, but may be entered into a computer program for in-depth data analysis. One can even send the data via telephone to a computer in the physician's office.

Factors in Deciding on Glucose Reflectance Meters

1. Portability
2. Ease of Use
3. Expense
4. Availability of Accessories
5. Quality of Technical Support
6. Insurance Coverage

These data management systems also have the capability of collecting and storing data on insulin doses, exercise, diet and other variables. Hand-held computers are also available which analyze the blood glucose readings and the amount of insulin taken and then suggest adjustments in insulin dosage. Such technology requires investment of several thousand dollars and not for every patient but for those few individuals who are highly motivated and interested. One should be cognizant of the reality that increasing sophistication of technology does not by itself lead to improved glycemic control.

INSULIN DELIVERY

Many innovations have been developed in this area, ranging from simple devices such as insulin pens to complex 'high-tech' implantable insulin pumps.

The pens look like fountain pens and reduce the amount of supplies needed for multi-dose regimens. The Novolin Pen (Connaught-Novo) can deliver 2-36 units of insulin per injection. Special vials of Novolin (regular, NPH and 30/70 regular/NPH) are available for use with the pen. Nordisk also manufactures a similar pen, called Insuject. These pens will be most helpful for Type II diabetics on a single type of insulin or for Type I diabetics on a regimen of Ultra-Lente and multiple doses of Regular insulin.

Insulin may be administered as a tiny stream forced through the skin under pressure rather than through a needle piercing the skin. Jet injectors were proposed over 35 years ago but there are continuing concerns regarding shorter duration of action of the insulin, increased antibody response to insulin, and the lack of information on the reliability of the injectors. More clinical study is necessary but a potential situation in which they may be of use is in patients with an extreme fear of the standard injections.

Insulin pumps deliver insulin through a small plastic tubing attached to a needle inserted under the skin. Only regular insulin is used. A pre-programmed basal dose of insulin is given throughout the day but boluses of insulin can be given whenever required (e.g. before a meal). The dosing of insulin is very precise and there is the potential of tighter glucose control. Also, the insulin pump would allow variety in scheduling of one's activities. However, to ensure success in using the pump, both the patient and the health care team must be well educated in diabetes; the patient must be well motivated with adequate insurance coverage and a good support system.

Two popular models that are available include the Betatron (CPI/Lilly) and MiniMed 504-S (MiniMed Tech.). The cost is approximately $4,000 and both companies offer 2 year warranties with options to trade in for a newer model if desired. The battery life is for one month on average and the whole pump weighs only 106 gm and is 5 × 9 cm in size. Patients considering pump therapy should be assessed by a diabetologist and nurses expert in diabetes, before embarking on such an investment. For patients judged to be appropriate for pump therapy, The Nova Scotia Diabetes Centre at the Halifax Infirmary site of the Camp Hill Medical Centre, currently has three MiniMed pumps which can be used on a trial basis.

Innovations in Insulin Delivery

Pens
Jet Injectors
Pumps

Currently, the type of glucose control available to diabetic patients is open-loop where the blood glucose is measured and then a decision is made regarding the dosage of insulin. There is active research in production of implantable insulin pumps which would offer even greater convenience. In the future, a closed-loop system, truly an artificial pancreas, will be available. Implantable glucose sensors will be directly connected to an insulin pump and thus insulin dosage will be automatically adjusted from minute to minute without requiring manual glucose monitoring or insulin adjustment.

It thus seems clear that management of diabetes mellitus will require understanding the technological advances in glucose monitoring and insulin delivery. We must also be aware that this technology should be used discriminately taking into account the patient's abilities and concerns. We must also remember that

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Patient Education in Management of Diabetes Mellitus

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People with chronic diseases must assume an active role in the day-to-day management of their care. To attain this important goal, they must acquire the knowledge and skills essential for self-care, an integral component of the management of their disease.

Diabetes mellitus is a chronic metabolic disease characterized, on the one hand, by derangements in carbohydrate, fat and protein metabolism and, on the other hand, by development of microangiopathy and macroangiopathy. Both components share in common hyperglycemia, the hallmark of diabetes. Each day the person with diabetes faces the challenge of minimizing the potential wide fluctuations of his blood glucose levels in order to prevent the acute complications of the disease — hypoglycemia and hyperglycemia (possibly associated with ketoacidosis in persons with Type I diabetes). Each day the person with diabetes endeavours to keep his blood glucose levels close to normal in order to minimize the chances of developing the debilitating long term complications of diabetes — retinopathy, nephropathy, neuropathy, coronary heart disease, cerebral vascular disease, peripheral vascular disease, and dermopathy.

The traditional three cornerstones in the foundation of a sound management plan for controlling diabetes are diet, hypoglycemic medications, and exercise. Patient education is now accepted as the fourth cornerstone of this foundation.

IS PATIENT EDUCATION NEW?

Patient eduation in diabetes is not a new concept. In 1919 Joslin, in his book entitled *A Diabetic Manual for the Mutual Use of Doctor and Patient,* stated "The manual . . . has been simplified with the reviewed purpose to make it serve as a textbook for the physician to use in the education of his patients".[1] In 1925 Lawrence, in his book entitled *The Diabetic Life: Its Control By Diet And Insulin. A Concise Manual For Practitioners And Patients,* stated "It is the object of this book to bring the modern treatment of diabetes by diet and insulin within the scope of the general practitioners and the understanding of the patients whose intelligent cooperation is necessary for the best results".[2]

THE NEED FOR PATIENT EDUCATION

The goals of diabetes care include the prevention of acute and long term complications associated with the disease. To attain these goals and to have a quality of life minimally compromised by the disease, persons with diabetes must assume an active role in the day-to-day management of their health care, serving as able assistants to skilled physicians and other health professionals. Usually the physician or other health professionals do not have direct contact with the average diabetic for more than 6 to 12 of the patient's 5800 waking hours per year.[3] Patients must be involved in developing the goals of treatment plans and acquire the knowledge and skills to implement them. The success of these plans depends, in a major way, on the patients' ability to respond appropriately to the changing demands of their body metabolism and their environment each day.

Studies in the 1950s and the 1960s documented a persistent lack of understanding of diabetes and its management among patients and their families.[4,5] While approximately 77% of all diabetics were placed on prescribed diets, only 10% had sufficient knowledge to choose the proper foods.[6] Among an insulin-dependent population, 60% made errors in insulin measurements and 65-90% of the patients had major problems in selecting the type of food and in adhering to prescribed meals and snacks. Less than 10% of the patients observed followed even minimally adequate regimens in all areas of their day to day diabetes management.[7]

EFFECTIVENESS OF PATIENT EDUCATION

Patient education is effective in decreasing both acute and long term complications of diabetes. In so doing, it reduces the cost of health care incurred by persons with diabetes.

Acute Complications

At the Grady Memorial Hospital in Atlanta, Davidson and his team of appropriately trained health professionals working in properly equipped facilities decreased the number of admissions due to diabetic ketoacidosis.[8] At the Los Angeles County Hospital, Miller and Goldstein introduced a telephone answering service and a screening of all candidates for hospitalization by the specially educated diabetes health care team and very significantly decreased the number of cases of diabetic ketoacidosis from 300 to 100 a year.[9] In Australia, Moffitt *et al* has also reported the efficacy of a diabetes teaching and treatment programme in reducing the frequency of acute metabolic deteriorations.[10]

Foot Problems and Amputations

At the Cantonal Hospital in Geneva four years after the implementation of a patient teaching and treatment

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programme, the number of below knee amputations decreased by more than 50%.[11] Both the Los Angeles County Hospital and the Grady Memorial Hospital programmes also decreased the number of foot problems in diabetics and, in so doing, decreased the number of amputations in persons with diabetes.

Hospitalization

Educational deficits had also been identified as a cause for hospitalization in persons with diabetes. Geller and Butler found that 27% of their patients had a specific education deficit and another 20% had both educational and psychosocio-economic problems responsible for their hospitalization.[12]

In the Joslin Clinic-New England Deaconess Hospital study of 100 consecutive admissions of persons with diabetes for foot problems, 34 admissions could have been prevented and another 41 might have been prevented.[13] In exploring further to determine the reasons for the hospital admissions, they discovered that 62% of the group had inadequate information about their diabetes.

The effect of out-patient diabetes education and treatment programmes on hospitalization rates had been demonstrated in many centres during the past two decades. In Maine, from 1978-1984, a 32% decrease in hospital admissions and a 29% decrease in hospital days for patients with diabetes were reported for 1488 patients during a 12 month period.[14] In Rhode Island there was a 50% reduction in diabetes-related hospitalization and a 63% decrease in emergency room visits of 217 patients attending the out-patient education programs from 1980-1984.[15] In Dusseldorf, Germany, a study on hospitalizations of patients before and after a diabetes teaching and treatment programme showed a significant decrease in admissions (0.8 *vs* 0.5 admissions/patient/year) and hospital days (16.7 *vs* 6.3 days/patient/year).[16]

Initiation of Insulin Therapy

Those persons with diabetes mellitus who depend on or require insulin for control of their disease have to be taught the complexities of this therapy. They have to learn the onset and duration of action of the different types of insulin, the techniques of withdrawing, mixing and administering insulin, the proper way of performing, documenting and interpreting blood glucose tests done at home, the appropriate guidelines to adjust insulin dose, diet and exercise in order to attain the goals of therapy on a day-to-day basis, and the many other challenges of living and being dependent on exogenous insulin each day.

In the past the rule was to admit these patients to hospital for initiation and education of insulin therapy. To-day, with the availability of outpatient education and treatment diabetes programs, admitting these patients for insulin therapy is the exception to the rule. Most of these adult patients can be managed on an out-patient basis, the preferred way as it incorporates the patient's daily routine in the treatment plan. The considerable cost saving in this practice is documented.[17]

Long Term Metabolic Control

Several studies have now documented improvement in long term glycemic control (as assessed by a decrease in Hb A_{1c}), as a result of participation in diabetes education and treatment programs.[18,19] Hopefully, this may lead to a decrease in the long term complications of diabetes.

Patient Compliance

To attain the goals of the diabetes management plan the patient must adhere to the prescribed therapeutic regimen requiring modification of existing behaviour (diet, exercise, etc) and development of new behaviour and acquisition of new skills (administering insulin, self-monitoring of blood glucose, adjusting insulin, diet and/or exercise, etc). The behaviour modification needed on a daily basis causes considerable emotional stress.[20]

Non-compliance is common in persons with diabetes — 50% of insulin treated persons with diabetes have been found to take the incorrect dosage.[7,21] Compliance with dietary therapy is also poor.[22,23] In elderly patients, compliance is a greater problem.[24]

Although the patient's lack of understanding of his disease was related to non-compliance,[6,23] providing information does not guarantee patient adherence to the prescribed regimen.[25] However, education programs have resulted in significant improvement in emotional well-being and self-care behaviour at six months and a year.[26]

Strategies to enhance patient compliance to the prescribed regimen in controlling diabetes include:

1) modifying the patients' health beliefs so that they will be more cooperative;
2) providing knowledge on the specifics of the treatment;
3) changing a complex series of behaviours one at a time and making the treatment regimen as simple as possible;
4) improving the health professional-patient relationship via better communication and understanding and support;
5) commiting to common therapeutic goals set by the health professionals and patients, making sure that both understand their roles and responsibilities;
6) Discouraging negative behaviours; reinforcing and rewarding positive behaviours promptly during monitoring of progress;
7) creating a supportive environment at home and at work by involving the patient's family and significant others in the implementation of the treatment plan;
8) minimizing the cost of the regimen;
9) providing regular follow-up in all important aspects of the treatment regimen; and
10) individualizing the treatment regimen and linking it with the patient's usual daily schedule.

A team approach through the diabetes education and treatment centre by health care professionals specially trained to deliver such health care provides the best opportunity to implement the above strategies to enhance compliance. In 1924, Joslin created the diabetes nurse educator and the diabetes wandering nurse, specialists who delivered the educational programmes in the hospital and at the homes of patients respectively.[27] Today, the diabetes health care team includes the physician, nurse educator, dietitian, social worker, clinical psychologist, occupational therapist and a few others. However, these health professionals serve as consultants to the most important member of the team, the person with diabetes who must live each day with his/her disease and implement the treatment plan.

Cost effectiveness

The total cost of diabetes in the United States in 1987 was estimated to be $20.4 billion.[28] The direct cost component a] Institutional (hospitals, nursing homes) was $7.87 billion and b] outpatients was $1.73 billion) was $9.6 billion. The indirect cost component (a] short term morbidity was $0.14 billion; b] long term disability was $3.14 billion; and c] mortality $7.49 billion) was $10.8 billion.

To be able to reduce this enormous socio-economic impact of diabetes to society will be a major achievement in health care delivery. There is no doubt that the cost of a diabetes health care team and the provision of appropriate and adequately-equipped facilities is considerable. However, compared with the health care dollars saved, it is modest and very reasonable. In 1972 the team at the Los Angeles County Hospital claimed a saving of $1.8 million over two years due to decreased hospitalization.[9] At the Grady Memorial Hospital, the team suggested that the hospital saved $3.7 million over a period of eight years (1971-1978).[8] In the Maine Study the net savings per participant per year was $293.[14] In the Rhode Island Study the estimated cost savings was $355 per participant per year to the health care system.[15]

At the Cantonal Hospital in Geneva over a 4 year period, 83 amputations were performed in persons with diabetes, but a 85% decrease of below knee amputations was achieved because of a specific foot care programme for persons with diabetes.[11] It was estimated that the cost of six below knee amputations (covering conservative medical treatment, surgery and the rehabilitation) was equal to that of the annual salary of the medical team at the Diabetes Teaching and Treatment Unit of the hospital (3 doctors, 4 nurses, 1 dietitian, 1 secretary, 2 assistant nurses and 1 cleaner). Thus, not only was it cost effective to run the Diabetes Teaching and Treatment Unit, but it also resulted in a better quality of life for the affected patient.

Quality and Quantity of Life

Although indisputable evidence is not in yet, it is generally accepted that the diabetic who is knowledgeable and skillful in controlling his disease has a better quality of life. Rubin *et al* recently demonstrated that those who have been educated had an improved emotional well being.[26] The patients who participated in the education program had less anxiety and depression whilst having greater self-esteem and diabetes self-efficacy.

Careful management of diabetes had been identified as a factor in the survival of patients with insulin-requiring diabetes for 50 years.[29] Persons with diabetes who benefitted from a global treatment plan had a 12 year longer life-span when compared with a group followed less regularly and who were less informed about their disease.[30]

DIABETES EDUCATION CENTRES IN NOVA SCOTA

Nova Scotians with diabetes are fortunate to have access to the resources of diabetes education centres in their regional or community hospitals. In Halifax, the Nova Scotia Diabetes Centre, based at the Camp Hill Medical Centre, has an education unit whose mission is "to provide high quality care to those adults affected by diabetes. . . . In order to achieve optimal health and/or alleviate complications, emphasis will be placed on self care and will be facilitated by patient education and psychosocial support." The NSCD's goals to promote self care of the person with diabetes include a) "developing a sense of responsibility and positive attitude towards the acceptance of his/her diabetes"; b) "increasing their knowledge and understanding of diabetes"; c) "assisting in the mastery of physical and problem solving skills"; and d) "incorporating the principles of adult education." The Diabetes Unit at the IWK Hospital for Children provides similar services but directed to children with diabetes and their parents. At the Grace Maternity Hospital a diabetes education program is available for pregnant women affected by diabetes. Throughout Nova Scotia, there is a network of similar diabetes education centres serving Nova Scotians affected by diabetes.

CONCLUSION

For people with chronic disease, patient education is an integral and important component of the management plan. Specifically for diabetes, patient education and regular follow-up by trained health professionals have facilitated the attainment of the treatment goals, the saving of health care dollars, the enhancement of patient compliance, and development of greater self-esteem.

In 1974 the American Hospital Association stated "patient education is an integral part of quality health care".[31] In 1976 the American Diabetes Association recognized the importance of patient education: ". . . good diabetic management necessitates education and training of both patients and health professionals in the techniques involved and close coordination and cooperation in patient management".[32] In 1980 the World Health Organization endorsed patient education

in diabetes: "Education is a cornerstone of diabetes therapy and vital to the integration of the diabetic into society."[33]

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DEVICES AND DIABETES MELLITUS

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these new techniques are not meant to replace physician contact but to supplement and maximize the benefit of the physician's care. □

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Research in the Division

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As an academic Division in the Department of Medicine at Dalhousie University, members of the Division of Endocrinology and Metabolism are involved in both basic and clinical research. There are five major areas of interest — diabetes mellitus, androgen metabolism, lipoprotein metabolism and atherosclerosis, hypertension and growth hormone deficiency. In this paper we shall summarize the research currently underway.

DIABETES MELLITUS

Our diabetes research focuses on three areas — insulin action and glucose metabolism, complications of diabetes and epidemiology of diabetes. Drs. Reddy and Tan are the two principal investigators and they collaborate with others in their search for new knowledge.

Insulin Action and Glucose Metabolism

Characterization of the Relationship of Alterations in Membrane Composition to Insulin Receptor Function in Diabetes Mellitus

Alterations in membrane lipid composition and evidence of multiple receptor defects have been found in the diabetic state. Modification of dietary fat can alter membrane lipid composition and insulin sensitivity in both *in vivo* and *in vitro* situations. The insulin receptor and other peptide growth factor receptors are integral cell membrane proteins; most of the current work on the insulin receptor has focused on the protein itself while relatively little work has been performed on the relevance of membrane lipids in membrane receptor function. Dr. Reddy is examining the nature of membrane alterations in diabetes by documenting lipid changes in plasma membranes of two major organs (liver and muscle) in animal models of diabetes mellitus, and relating these changes to insulin action. He is also studying hormone action in cultured cells and in isolated receptors by modifying their membrane composition with gangliosides, lipoproteins and lipids. These findings may eventually have a major public health impact by possibly leading to dietary or pharmacological manipulation in an effort to improve insulin sensitivity in diabetes mellitus.

Relevance of Heat Shock Protein in Insulin Action

Heat shock proteins (HSP) are proteins whose synthesis are stimulated by exposure of cells to an increase in temperature. They are present in all levels of life forms, and their functions have yet to be clearly delineated. HSP-90 (90 kilodalton molecular weight) is acutely increased by insulin. There is growing evidence the HSP-90 regulates steroid receptor function and may regulate tyrosine kinases, suggesting that it may be a common regulator of receptors of several types of hormones. Dr. Reddy plans to further characterize this insulin associated phenomenon and attempt to determine the physiological relevance of this phenomenon to insulin action.

Differential Effects of Highly purified EPA and DHA on Insulin Action and Membrane Lipid Composition

Despite the potential beneficial effects on cardiovascular disease, the clinical use of fish oil is controversial, especially in the treatment of dyslipidemia in diabetes mellitus. The variable effects are due to the great variety of types of preparations of fish oils used in medical research. They contain omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], and there has been little research on their effects separately. In collaboration with Dr. R. Ackman and C. Parrish of the Technical University of Nova Scotia, Drs. Reddy and Tan plan to study the individual effects of EPA and DHA on insulin action in rat hepatoma cells which are rich in insulin receptors and in skeletal muscle, the major organ of glucose utilization. Both EPA and DHA can modify the lipid composition of plasma membranes in cells and the potential clinical impact of this research is as outlined above.

Glucose Transport in Skeletal Muscle

The binding of insulin with its receptor on the plasma membrane of skeletal muscle cells triggers several biochemical processes, including glucose transport, glycolysis and glycogenesis within the myocytes. There are two major pools of glucose transporters — the plasma membrane and the low density microsomal pools. After insulin binds with its receptor, there is translocation of the glucose transporters from the intracellular low density microsomal to the surface plasma membrane pool. The increased number of glucose transporters on the surface then transports glucose into the cell. Physical activity (exercise and inactivity) affects glucose transport. In collaboration with Dr. A. Bonen of the School of Physical Education at Dalhousie University, Dr. Tan is studying the mechanisms of changes of the glucose transporters as a result of changes in physical activities. Their findings can lead to a better understanding of how exercise alters

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the insulin sensitivity of skeletal muscle, the major user of glucose in the human body.

Alpha Glucosidase Inhibitors and Diabetes Control

The post-prandial increase in blood glucose is influenced by many factors, including the rate of breakdown of complex to simple carbohydrates. Acarbose®, an alpha glucosidase inhibitor, slows down this digestive process. Dr. Tan is currently participating in a Canadian multicentre, randomized, double blind study evaluating the efficacy and safety of Acarbose® on the control of blood glucose in persons with Type II diabetes.

Complications of Diabetes

Angiostatic Steroids and Diabetic Microvascular Complications

About 20% of diabetic patients do not develop microvascular complications, despite many years of poor glucose control. They seem to be protected and may have genetic or acquired protective factors. One such factor may be naturally occurring angiostatic steroids which inhibit angiogenesis in the absence of heparin-like molecules. Microangiopathy is uncommon before puberty. Drs. Reddy and Salisbury plan to document urinary excretion of the most potent naturally occurring angiostatic steroid at various stages of puberty in normal and diabetic children. Their findings may lead to a better understanding of the development of microvascular complications.

Aldose Reductase Inhibitors and Diabetic Retinopathy and Nephropathy

The increase in sorbitol and the concomitant decrease in myoinositol have been linked to the development of microangiopathy (retinopathy, nephropathy and neuropathy) in diabetics. The conversion of glucose to sorbitol is catalysed by aldose reductase. The activity of this enzyme can be inhibited by aldose reductase inhibitors and Tolrestat®is one of many drugs having this action. A multicentre Canadian study on the effect of Tolrestat® on the progression of retinopathy and nephropathy in diabetics is underway. Dr. Tan is the principal investigator for the Halifax Centre and his co-investigator is Dr. V. Kuzousek of the Department of Ophthalmology.

HMG-CoA Inhibitors and Diabetic Macroangiopathy

Dyslipidemia is a common cardiovascular risk factor in persons affected by diabetes. Although hypertriglyceridemia is more prevalent, hypercholesterolemia is also present. A possible cause for the elevation of plasma cholesterol is the decreased catabolism of glycosylated low density lipoproteins (LDL) by LDL receptors. The HMG-CoA reductase inhibitors increase the numbers of LDL receptors on the cell surface and, in so doing, enhances LDL catabolism. Dr. Tan is participating in an international multicentre study determining the efficacy of Pravastatin, a HMG-CoA reductase inhibitor, on hypercholesterolemia in persons with Type II diabetes.

Epidemiology of Diabetes Mellitus

Insulin-dependent diabetes mellitus (IDDM) is one of the most common important chronic diseases of children world-wide. In industrialized countries, it is among the most prevalent chronic childhood diseases. Even in children, IDDM has significantly increased morbidity and mortality, as well as an enormous socio-economic impact on society when compared with the non-affected population. Because of the limited available information, a World Health Organization (WHO) Multinational project for childhood diabetes (Diabetes Mondiale or DIAMOND) has been started. The objective is to collect accurate, population-based data concerning IDDM worldwide to the year 2000. Two Canadian centres have been invited to participate in this study and Dr. Tan is the principal investigator from Dalhousie University.

ANDROGEN METABOLISM

Dr. Rittmaster's research concerns the adverse effects of androgens (male hormones) in women and men. In women, androgens can cause hirsuitism, acne, and scalp hair thinning ("male-pattern" baldness), and can lead to the development of the polycystic ovarian syndrome. In men, androgens cause benign prostatic hyperplasia (BPH), prostate cancer, and male-pattern baldness.

Hirsutism

Testosterone is the major androgen in blood. To be active in the skin and prostate gland, testosterone must first be converted to dihydrotestosterone by the enzyme 5α-reductase. Androgens arise from both the ovaries and the adrenal glands. Dr. Rittmaster has found that hirsute women with regular menses have a predominantly adrenal source of their androgens, while women with irregular menses have a predominantly ovarian source. Two androgen conjugates which are increased in hirsute women, androstanediol glucuronide and androsterone glucuronide, primarily reflect the adrenal component of androgen secretion. The fact that these two conjugates are elevated in most hirsute women suggests that these women, as a group, produce excess adrenal androgens (as well as excess ovarian androgens in some women).

Hirsutism can be a psychologically devastating condition. Dr. Rittmaster has been investigating which medical treatments work best for hirsute women. Antiandrogens (androgen receptor blockers) such as spironolactone (Aldactone®) and cyprosterone acetate (Androcur®) are effective in reducing hair growth in at least 75% of women. The remaining women do not become worse, while the natural history of hirsutism in most women is to become gradually worse with time.

On the other hand, birth control pills and glucocorticoids are largely ineffective in reducing hair growth, although they may stabilize the problem. Medications such as leuprolide, which turn off the ovaries, are effective treatments for women with polycystic ovarian syndrome.

Benign Prostatic Hypertrophy and Baldness

While antiandrogens might prevent these problems, they would also cause impotence and gynecomastia because they block both testosterone and dihydrotestosterone. A new class of drugs, 5α-reductase inhibitors, inhibit only dihydrotestosterone formation, and offers a possible treatment for BPH and male-pattern baldness. Dr. Rittmaster is now investigating one such inhibitor, finasteride (Proscar). Currently he and Dr. Richard Norman (Urology) have enrolled 30 patients with BPH in a multicenter trial. The effect of finasteride on hair growth is also being assessed. In a series of basic science and clinical studies, partly in collaboration with Dr. Catherine Lazier (Biochemistry), they are also investigating the effect of finasteride on prostate and pituitary physiology.

LIPOPROTEIN METABOLISM AND ATHEROSCLEROSIS

One of the major risk factors for coronary heart disease (CHD) is dyslipidemia (elevated LDL cholesterol and/or reduced high density lipoprotein (HDL) cholesterol). Dr. Tan is currently involved in a multicentre study evaluating the efficacy and safety of a new HMG CoA reductase inhibitor, Pravastatin, measuring its effect on the plasma LDL and HDL-cholesterol.

Changes in the composition of the lipoprotein particle may alter its atherogenicity. It consists of a core of neutral lipids (cholesteryl esters and triglycerides) enveloped by a membrane composed of free cholesterol (FC), phospholipid (PL) and apoproteins. An increase in the FC/PL molar ratio has been observed in patients with atherosclerosis. This alteration has been shown to alter a chemical gradient resulting in an impairment in reversed cholesterol transport from the peripheral cells to the liver. Dr. Tan is studying the effects of various hypolipemic drugs on this novel lipid risk factor.

An increase in the apoprotein Lp(a), which has structural similarities with plasminogen, is now regarded as a risk factor of CHD. Together with Dr. C. Breckenridge of the Department of Biochemistry, Dr. Tan is studying the effects of various hypolipemic drugs on this apoprotein.

Several drugs can raise serum lipid levels. One such drug is Amiodarone, an antiarrhythmic drug. Drs. Tan and Tim Pollak are studying the changes in plasma FC/PL molar ratio, Apo B/A-I mass ratio and, Lp(a) levels in patients taking Amiodarone.

HYPERTENSION

The fourth area of research interest is hypertension. Dr. Abbott participates in several multicentre trials evaluating the efficacy, safety and other aspects of new antihypertensive drugs. The Alpha-Beta Canada (ABC) Study compares the alpha-1 blockade with Doxazosin and selective beta-1 blockade with Atenolol in a risk modifying approach to the management of uncomplicated mild or moderate hypertension. The objective is to compare the efficacy, adverse effects and compliance of patients on either of these two agents as well as to assess the effects of either agent on serum total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

Two other new anti-hypertensive drugs, Carvedilol (a non-cardioselective beta blocker with vasodilating properties) and Cromakalim (BAL 34915) (a drug that alters the movement of potassium in and out of the vascular muscle cell and alters the rate and degree of repolarization) are being similarly studied.

Dr. Abbott is also collaborating with other physicians in studying various aspects of care of the hypertensive patients. Together with Dr. L. Kirby, he is studying the effect of beta-blockade on cardiac-locomotor coupling during locomotion. Fatigue and impaired exercise tolerance, common effects of some beta-blockers, may interfere with the normal coupling of cardiac muscle contraction and step (walking, running) rate. They plan to test the hypothesis that some beta-blocking medications affect this physiological coupling.

Together with the staff of the Clinical Psychology Department and the Multiple Sclerosis Unit of Camp Hill Medical Centre, he is searching for possible cognitive deficits, sometimes found in hypertensive patients, in patients with multiple sclerosis by using a broad-based assessment of quality of life and comprehensive neuropsychological assessments.

GROWTH HORMONE DEFICIENCIES

Dr. Salisbury, a member of the Canadian Growth Hormone Advisory Committee, is involved in several multicentre trials testing the efficacy and safety of recombinant DNA growth hormone. The Canadian Therapeutic Trial to investigate the safety and efficacy of DNA growth hormone (GH) (Humatrope®, Eli Lilly) (Abitropin, ABI Biotechnology Inc.) have now been completed. Efficacy of increased frequency of administration, maintaining the same total weekly dose is now being studied. GH deficient children (prepubertal) are given GH either 3 times or 6 times weekly with a crossover after 1 year between groups.

A trial to study the efficacy of GH (Humatrope®) in Turner's Syndrome is now underway. The usefulness of GH (Abitropin) in prepubertal children with chronic renal failure and short stature or marked decrease in growth velocity is also being studied.

OTHER RESEARCH

Dr. Givner, in collaboration with M. Comeau, Drs. E.M. Gimenez-Q, G.W. Bethune and B.J. Steele, have

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Postpartum Psychiatric Disorders in Nova Scotia

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The postpartum period is a time of increased risk for emotional disorders. The purpose of this study was to ascertain the frequency of recognized postpartum depression and postpartum psychosis in Nova Scotia. Records from the Nova Scotia Department of Health were cross-referenced for all women who gave birth between June 1, 1985 and May 31, 1986 and who were also treated for psychiatric disorders within one year postpartum. The frequency of postpartum depression was found to be 7/1000, significantly lower than the expected 10%. Reasons for this discrepancy include the inaccessibility of records for all cases of postpartum depression. The underrecognition of this disorder may also be a factor, as the Nova Scotia Department of Health records include only hospital admissions, and community and outpatient clinic visits. The frequency of psychosis within three months postpartum was, as expected, 1/1000. This is primarily because most cases were hospitalized and were therefore contained in the available records. An analysis of the types of depression and psychosis was also performed. However, this revealed few trends.

The postpartum period is a time of increased risk for psychiatric disorders.[1-5,8] In addition to the emotional suffering experienced during the episode, a series of long term effects may ensue, including ongoing disruptions in both marital and family relationships [5] and long lasting emotional effects on children.[6,7] It is, therefore, important that health care professionals realize the frequency of postpartum psychiatric disorders and learn to recognize and to treat them.

PURPOSE

The purpose of this study was to review the Nova Scotia Department of Health records in order to estimate the frequency of psychiatric illness in the postpartum period. This estimation of frequency could then be used to plan services for psychiatrically ill postpartum women.

REVIEW OF THE LITERATURE

There are three major categories of postpartum emotional disorders:

1) Postpartum Blues
2) Postpartum Depression
3) Postpartum Psychosis

Postpartum Blues

Postpartum blues usually begin within the first week and are often evident by day 3-4. The "blues" may last only one or two days or as long as two weeks.[5] The features include transient depressed mood or mood lability, tearfulness, feelings of inability to cope with mothering and mild confusion. However, the "blues" are short lived and will spontaneously resolve with support and reassurance.[5] Postpartum blues occur very commonly with the frequency ranging from 34-84%.[9] Due to the relatively mild nature of the symptoms and the short duration of postpartum blues, the syndrome was not investigated in this study.

Postpartum Depression

Postpartum depression is more severe and debilitating than the blues. Onset can occur within a few weeks of giving birth or up to 9-12 months postpartum.[10] The symptoms are the same as for any major affective disorder, as described in DSM III R.[11] Disturbed sleep and lack of energy are present to a greater degree than would be expected with a new infant. In addition, symptoms of loss of interest in the baby or paradoxically, overconcern with the infant, feelings of worthlessness and self-reproach, and even thoughts of suicide or of harming the child may be present.[1,5] Incidence rates cited in the literature range from 3-45% of all postpartum women; the most common figure being 10%.[1,3,9,12-14]

Postpartum depression benefits from early treatment to prevent a prolonged course of the illness and a negative impact on the child and family.[6,7] Gjerdingen found that if untreated, many women had depression lingering for more than one year postpartum.[7] Recurrences occur in approximately 30% of subsequent pregnancies.[15]

Postpartum Psychosis

Postpartum psychosis characteristically presents with rapid onset of symptoms, excited behaviour, confusion, hallucinations and delusions, which may include the infant.[1,5,10] There is a very real risk of infanticide or suicide.[5] Onset is typically within the first six weeks postpartum and usually requires hospitalization.[5] The incidence of postpartum psychosis is consistently cited cross-culturally as being 1-2 cases per 1000 deliveries.[1,3,9,12,13]

METHODS

Records from the Nova Scotia Department of Health were cross-referenced for all women who gave birth between June 1, 1985 and May 31, 1986 and who were

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also treated for psychiatric disorders within one year postpartum. "Psychiatric treatment" included admission to a psychiatric hospital, admission to a general hospital with a psychiatric diagnosis, or psychiatric outpatient treatment. Data on visits to a family doctor or private psychiatrist were not available through Medical Services Insurance (MSI).

The diagnoses submitted to the Department of Health had been classified according to ICD-9.[16] No discreet category for postpartum disorders was contained in this classification or in the widely used DSM III-R.[11] The ICD-9 diagnoses were therefore divided as seen in Table I.

TABLE I

CLASSIFICATION OF ICD-9 DIAGNOSES

1. **Postpartum "Depression"**	— Adjustment reactions — Neurotic disorders — Depressive disorders
2. **Postpartum Psychoses**	— Non-organic psychosis — Reactive confusion — Organic psychosis — Schizophrenic disorders — Manic-depressive disorders — Affective psychosis
3. **Not Considered Postpartum Disorders**	— Reaction to stress (without qualifying diagnosis) — Personality disorders

Admissions were considered to be in the broad category of postpartum depressive disorders if they occurred within one year of parturition and were classified in ICD-9 with the major diagnosis of "depression." These depressions fell into the categories of adjustment disorders, neurotic disorders or depressive disorders. Out of the total of 185 cases, 75 with diagnoses of personality disorders or diagnoses too vague to classify were excluded from the category of postpartum depressions (i.e., personality disorder with hysteria as the only diagnosis). Although postpartum depression often has an onset within six weeks of childbirth, the illness is frequently not recognized by the patient or physician and therefore is untreated for prolonged periods, up to one year.[1,2,5,10,12,13] Therefore, a diagnosis of depression within one year of giving birth was the criterion used for establishing postpartum depression in this study.

Postpartum psychoses most frequently have an onset within 4-6 weeks after delivery.[5,18] Due to the severity and acute nature of this disorder, admission to hospital occurs quickly, and thus most are recorded within three months postpartum.[10] Therefore, the admissions were divided into two groups — psychosis admitted before three months postpartum and the remainder, admitted from 3-12 months postpartum.

The incidence of both postpartum depression and postpartum psychosis was calculated by dividing the number of postpartum psychiatric cases in each category by the number of births for the year.

RESULTS

There was a total of 110 cases receiving psychiatric treatment, falling into the category of either postpartum depression or psychosis within one year of delivery in the above facilities. The number of deliveries in Nova Scotia for this time period, according to the Department of Health, was 12,381.

The estimate of recognized postpartum depression seen in Nova Scotia Department of Health facilities was calculated to be 7/1000. The estimate of psychosis within three months postpartum was 1/1000 and the rate for psychosis for 3-12 months postpartum was also 1/1000.

In analyzing the types of postpartum depression, according to ICD-9,[16] Depressive disorders represented 46%, while Neurotic disorders comprised 33% and Adjustment disorders, the remaining 21%.

Psychoses prior to three months postpartum were divided as follows: 50% manic depressive disorders, 17% organic psychoses, 17% affective psychoses, 8% non-organic psychoses, and 8% reactional confusion. Schizophrenia was not represented prior to three months postpartum.

From 3-12 months postpartum, manic depressive disorders comprised 55% of the psychoses, schizophrenia 27%, organic psychoses 9%, and non-organic psychoses 9%. Affective psychosis was not found.

DISCUSSION

The computed frequency of postpartum depression in Nova Scotia, using Department of Health figures, was very low, 7/1000, compared to the average estimate in the literature of 10%.[1,3,5,9,12,13] Since it has been shown that the incidence of postpartum disorders is consistent cross-culturally, it would seem unlikely that there are fewer women with postpartum depression in Nova Scotia.[4,12,17,18] The discrepancy can be explained by the large proportion of women who were either never recognized as having a postpartum depression, or who sought help through their family physician or private psychiatrist. The statistical information available from the Nova Scotia Department of Health did not permit tracing of patients visiting family physicians or private psychiatrists. Thus, the calculated frequency of postpartum depression was underestimated. In addition, it has been found that a large proportion of depressions remain unidentified and this will contribute to the underestimation of the incidence of postpartum depression.[1,19]

Postpartum depression can be underrecognized for a variety of reasons. The illness most commonly begins following discharge from hospital and since the first postpartum visit to the physician is four to six weeks later, psychiatric illness can develop and go unrecognized during this period.

Further, postpartum depression is often not recognized as health care professionals have received little education regarding the signs, symptoms and frequency of postpartum disorders. A recent sampling of Nova

Scotia physicians at a Continuing Medical Education conference supports the hypothesis that physicians are significantly underestimating the frequency of postpartum depression.[20] Information from prenatal classes and popular magazines emphasizes the positive and idealized concept of motherhood. Mothers often feel inadequate and guilty if they admit they are depressed and consequently may not seek help. Therefore, it is the caregiver who has to be aware of risk factors, inquire about emotional problems, and be sensitive to cues regarding the mother's emotional and physical well being. Many of the symptoms of postpartum depression are overlooked because of the expected physical changes that occur normally postpartum (eg., insomnia, weight loss and fatigue).

The calculated frequency for postpartum psychosis was 2/1000 during the entire first year, which is within the range of 1-2/1000 found cross-culturally.[1,3,5,8,9,12,19] The acute onset of psychosis requires immediate medical attention and admission to hospital. Since the Department of Health data included all postpartum hospitalizations, the majority of cases were expected to be included in our study. The number of psychoses recorded from 3-12 months postpartum is surprisingly high, since most studies report the highest incidence in the first three months postpartum.[3,10,12]

In analyzing the types of psychoses found in the postpartum, no trends were obvious. However, studies were difficult to compare due to different classifications of diagnoses. A study reviewed by Gjerdingen found that 68% of postpartum psychoses could be classified as affective psychoses, 28% schizophrenic disorders, and 4% organic psychoses.[1] These results do resemble the frequencies of diagnoses found in this study (Table II).

TABLE II

ANALYSIS OF POSTPARTUM DISORDERS ACCORDING TO DIAGNOSIS

1. Postpartum "Depression" (n=87)

Diagnosis	Number	Percentage
Depressive disorders	40	46%
Neurotic disorders	29	33%
Adjustment disorders	18	21%

2. Postpartum Psychosis (n=23)

	0-3 months (n=12)		3-12 months (n=11)	
Diagnosis	No.	%	No.	%
Manic depressive disorders	6	50%	6	55%
Organic psychosis	2	17%	1	9%
Affective psychosis	2	17%	0	0%
Non-organic psychosis	1	8%	1	9%
Reactive psychosis	1	8%	0	0%
Schizophrenia	0	0%	3	27%

The main methodological difficulty encountered was the necessity of reclassifying ICD-9 diagnoses into postpartum depression and postpartum psychosis (Table II). No discrete codes existed for postpartum disorders, thus, some interpretation of the codes was required. In addition, the Department of Health statistics are obtained by translating the physician's diagnoses into ICD-9 codes. This is often done by clerical staff who may lack the background for detailed interpretations of diagnoses. Staff at various hospitals may code diagnoses differently leading to further inconsistency in the Department of Health statistics. Therefore, our study was limited by the reliability of the Department of Health statistics available and the lack of discrete coding for postpartum disorders, in addition to the lack of data from family physicians and private psychiatrists.

CONCLUSION

The frequency of postpartum depression during the first year using Nova Scotia Department of Health statistics, was found to be 7/1000, significantly lower than the expected 10%. Reasons for this discrepancy include the inaccessibility of records for all cases of postpartum depression and the underrecognition of the disorder. To estimate a more accurate incidence of postpartum depression, either a prospective study or a retrospective study utilizing case notes and all health care records would need to be undertaken.

The frequency of postpartum psychosis was as expected, 2/1000, largely because most cases were hospitalized and were therefore contained in our records.

Postpartum psychiatric disorders are becoming recognized as frequent complications of the postnatal period. Awareness of the frequency of psychiatric problems in the postpartum may promote early identification and treatment of affected mothers. This, in turn, may reduce emotional suffering for the mother, the family and the baby. □

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Successful Treatment of Antidepressant-Induced Akathisia with Amantadine.

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Akathisia is a well-known neuroleptic-induced side effect with particular subjective motor complaints and observable findings. In this case presentation, a patient developed similar symptoms subsequent to the initiation of antidepressant medications. His motor complaints resolved with the use of amantadine, known as an effective treatment for akathisia. We suggest that the tremor and minor motor restlessness, which are seen quite commonly with antidepressants, may be on a continuum with akathisia.

In 1903, Haskovec coined the term "akathisia" to describe a motor restlessness which, he felt, was hysterical in origin. This symptom has been well known to be one of the group of extrapyramidal side-effects secondary to neuroleptics. Its clinical objective findings and subjective experiences have been variously documented, but the neurophysiological basis remains an enigma. This symptom is very disturbing to patients and occurs frequently, in from 12.5% to 75% of neuroleptic users.[1] A study by Ayd of 3,775 patients revealed an incidence of 21.2% who developed neuroleptic-induced akathisia and this figure is similar to most of the current data.[2]

The feelings reported by patients are variously described as "muscular quivering", "a motor with an uncontrollable drive", "a craving" and "an inability to sit still". Clinical physical observations should, however, be made concurrently which might reveal someone who has psychomotor agitation, is fidgeting, having a shuffling posture, tapping feet, easily provoked into anger, or having emotional lability.[3] The amount of distress can gain such momentum that the patient becomes impulsively suicidal.[4]

This report illustrates the case of a patient who was initially treated with clomipramine, an antidepressant drug and then developed akathisia.

CASE REPRESENTATION

Mr. F., a 28 year old single adopted man, presented to the emergency room with symptoms of anorexia, mild weight loss, terminal insomnia with frequent wakenings, anhedonia, decreased energy, concentration and functioning at work, and depressed mood with suicidal ideas. He was neither deluded nor hallucinated. He had been abusing alcohol and cannabis for many years. There was a prior history of an overdose at the age of 19 and a possible depression at age 12. Ongoing stressors included difficulties between his adoptive and natural parents and some financial problems. His medical history revealed inactive Crohn's disease and mild asthma. The patient's biological parents had no significant physical or psychiatric history. A diagnosis was made of a major depressive episode, unipolar type (by DSM-IIIR Criteria) as well as of cannabis and alcohol dependence.

The patient was started on clomipramine and after four weeks had significant resolution of his depressive mode and neurovegetative features. Two days prior to discharge, on a dose of 175mg/day, he began to develop some minor motor restlessness with obvious fidgeting but no dysphoria. After discharge, he was steadily pacing and unable to sit still. The dosage of clomipramine was decreased to 150mg/day without effect. His motor complaints remained distressing for several days and he was finally rehospitalized. Clomipramine was gradually discontinued and finally stopped.

Clonazepam, a high potency benzodiazepine, was begun and gradually increased up to 10 mg daily. His motor restlessness cleared and the clonazepam was tapered and gradually discontinued. With the onset of the patient's depressive features gain, maprotiline was begun and gradually increased to a therapeutic dosage; due to a resumption of his motor distress, amantadine was started at a dose of 100 mg b.i.d. Unfortunately, the patient developed a grand mal seizure on 225 mg/day of maprotiline and this antidepressant was switched to desipramine, slowly progressively increased. When the amantadine was stopped on the eighth day, the same aggravating symptoms returned, so it was reinstituted. Mr. F. was subsequently discharged in good condition, on desipramine 175 mg a day in addition to the amantadine.

Routine random street-drug screenings while in hospital were negative and all antidepressant blood levels were within the alleged therapeutic ranges. The patient did not develop any other iatrogenic effects from his medications and biochemical results were within normal limits. The patient's presentation and symptoms during his hospital stay did not include any euphoric or manic feature.

DISCUSSION

In this case presentation, some alternative differential diagnoses should be considered in view of Mr. F.'s unusual symptomatology. For instance, the possibility that an antidepressant may have triggered a hypomanic spell is unlikely since Mr. F. neither had any of the

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features of a bipolar disorder nor was his personal background or family history consistent with this hypothesis.[5,6] A withdrawal syndrome from alcohol or cannabis is also unlikely since the patient's motor restlessness presented four weeks after admission, well beyond the usual period for occurrence of withdrawal symptoms. Random street drug testing confirmed that the patient was not indulging in illicit substances while in hospital. However, it has been reported that active metabolites of cannabis may persist in the body (detectable in urine samples) for more than a month, even after a single dose.[7]

Although unlikely, a hypothesis of late cannabis withdrawal may be raised in the case of Mr. F. who was using large amounts of cannabis prior to his initial hospitalization. We also considered the possibility that the patient was using alcohol and cannabis in an attempt to mask an anxiety disorder which may have been reactivated following discontinuation of these substances. We felt that the previous two hypotheses were unfounded based on conclusions explained below.

From a clinical standpoint the patient had clear symptoms of a major depressive disorder with obsessional feelings of guilt and isolation. The pronounced obsessionality guided our choice of clomipramine.[8] Although motor restlessness has been reported with tricyclic antidepressants,[9,11] this akathisia-like syndrome came to our interest when Zubenko reported five cases with this type of presentation and showed that a wide variety of antidepressants were involved.[12] He implicated imipramine, desipramine, trazadone and tranylcypromine. This was consistent with our findings in that each of the three antidepressants used in the case of this patient caused a syndrome compatible with akathisia, regardless of their serotonin or norepinephrine reuptake blocking properties. It should also be noted that the patient's motor restlessness occurred initially two to three weeks after initiation of therapy which is compatible with the neuroleptic-induced form of akathisia.[13]

Use of anticholinergic or antihistamine agents in treating neuroleptic-induced akathisia has proved usually to be somewhat ineffective. Therapeutic approaches nowadays include: a) decreasing the dosage of the neuroleptic agent; and/or b) the addition of propranolol;[14-15] c) a benzodiazepine;[16] or d) amantadine.[17-18] Propranolol, a beta adrenergic blocking agent, usually very effective in the treatment of akathisia, could not be used to its usual level due to the patient's asthma. Clonazepam, an extremely potent benzodiazepine, most likely acting through GABA potentiation, proved to be effective in stopping Mr. F.'s symptoms, but this coincided with the time that the antidepressant was stopped. In fact, when clonazepam was discontinued, there was no rebound of anxiety which is consistent with the belief that we were not dealing with a primary anxiety disorder mimicking akathisia. In the case of this patient, amantadine was effective in eliminating his motor agitation.

The possibility that Mr. F.'s symptoms were secondary to a cannabis withdrawal syndrome appears unlikely since when the amantadine was withdrawn the patient's symptoms recurred, suggesting a direct effect of amantadine in relieving Mr. F.'s restlessness.

Mr. F.'s clinical presentation and response to treatment seemed to be almost identical to that of neuroleptic-induced akathisia. The patient had entirely similar subjective symptoms; and his behaviour, as observed by us, was strikingly similar to that of patients with neuroleptic-induced akathisia. It seems possible that the tremor and minor motor restlessness noted quite often to occur with tricyclic antidepressant drugs may be on a continuum with akathisia. Clearly, more research into this field is necessary, especially to assess the neurophysiological basis of this syndrome. □

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The Anemic Patient with Hyposplenism

A CLUE TO THE PRESENCE OF OCCULT GLUTEN-SENSITIVE ENTEROPATHY

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Gluten-sensitive enteropathy is a disorder in which the villi of the small bowel atrophy, leading to variable malabsorption of fat, protein, essential vitamins and trace elements. Affected patients usually experience anorexia, weight loss, abdominal bloating, diarrhea, or steatorrhea. In certain individuals the disorder may be occult. We have recently seen two asymptomatic patients with anemia and peripheral blood smear findings suggesting hyposplenism (Howell-Jolly bodies, acanthocytes and target cells). Serum ferritin and red cell folates were reduced in both patients. Neither had symptomatology suggestive of gastrointestinal malabsorption and both had normal serum levels of albumin, total protein, calcium, vitamin B_{12} and carotene. In spite of lack of symptoms or laboratory data suggestive of malabsorption, the strong association between functional hyposplenism, anemia, and gluten-sensitive enteropathy led to duodenal biopsies being performed, confirming villous trophy in both cases.

Gluten-sensitive enteropathy (nontropical sprue, coeliac disease) is a disease characterized by small bowel villous atrophy. It frequently results in diarrhea, weight loss, steatorrhea and malnutrition but in some the symptoms are more subtle. Affected individuals may present with isolated vitamin deficiencies and no gastrointestinal symptoms.[1,2] Hyposplenism as diagnosed by screening red cell morphology is reported to occur in only one-third of the cases of coeliac disease.[3-7] Thus its recognition in an asymptomatic individual is crucial and may lead to a suspicion of the diagnosis of nontropical sprue. This report details two patients who had no symptoms or laboratory evidence of malabsorption but were found to have occult gluten-sensitive enteropathy during the investigation of isolated anemia and defective splenic function.

CASE PRESENTATIONS

Case 1

A 65-year-old female was admitted to hospital for urological investigations. Earlier, she had been diagnosed as having interstitial cystitis when cystoscoped for evaluation of persistent frequency. Pertinent past medical history included a vague history of "anemia" in 1960 for which she was treated with parenteral iron. Four months prior to this admission, her family doctor had noted her to be anemic and prescribed iron and folate supplements. Nor further investigations were done.

At the time of admission, the patient's most pressing complaint was urinary frequency. On functional inquiry she admitted to a two month history of anorexia but denied weight loss. She gave no history of diarrhea, constipation, abdominal pain or bloating, melena or rectal bleeding. Her only medications were slow Fe, folic acid and L-thyroxine for hypothyroidism diagnosed in 1964. The patient had three healthy children but because she herself was adopted, no other family information was available.

Physical examination was normal aside from a shortened left leg with pes cavus deformity secondary to childhood poliomyelitis. Laboratory investigations showed her hemoglobin to be 96 g/L (normal 115 to 155), mean corpuscular volume was 79 fL (normal 80 to 97), white blood cell count was 8.1×10^9/L (normal 4.5 to 10.5) with a normal differential, and platelet count was 550×10^9/L (normal 150 to 350). Red cell morphology was abnormal with marked anisocytosis, acanthocytes, target cell and Howell-Jolly bodies being present. Serum levels of urea nitrogen, electrolytes, albumin, total protein, clacium, carotene, SGOT, SGPT and total bilirubin were normal. Serum ferritin was decreased at 7 µg/L (normal > 10). Serum folate was 2.7 nmol/L (normal > 5.5) and red cell folate 155 nmol/L (normal > 265). Serum B_{12} was normal. Bone marrow aspirate revealed absent iron stores but erythropoiesis was normoblastic. Stools for occult blood were negative on two occasions. Upper GI series with small bowel follow through showed a normal mucosal pattern with a small hiatal hernia. Barium enema was normal. A liver/spleen scan was consistent with splenic atrophy (span of 5.2 cm). The patient was discharged on slow Fe and folic acid.

Although the patient had no symptoms or laboratory evidence of gastrointestinal malabsorption, the strong association between a combined folate and iron deficiency anemia, hyposplenism and coeliac disease led to further investigations. A D-Xylose absorption test was performed and was abnormal with 2% of the ingested dose excreted in the urine in five hours (normal 16-36%). Upper GI endoscopy was normal but duodenal biopsy showed villous atrophy consistent with gluten-sensitive

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enteropathy. She was started on a gluten-free diet and in followup one year later, her hemoglobin was 121 g/L. She had gained 18 pounds and complained only of occasional constipation.

Case 2

Three years ago, a 35-year-old woman was found by her family doctor to be anemic, with a hemoglobin of 90g/L. Her serum folate level was reduced and she was started on replacement folate therapy which was continued for one year. One year later she presented with fatigue and was found to have a hemoglobin of 109 g/L with mean corpuscular volume of 104 fL. Serum iron was reduced at 4.1 μmol/L (normal > 7.2) with a total iron binding capacity of 66.6 μmol/L (normal 44.8-71.6). There was no history of gastrointestinal blood loss and she consumed a healthy, balanced diet. She admitted to heavy menstrual bleeding with the occasional blood clot passed. She was started on ferrous sulfate 300 mg po TID but because of persistent fatigue she was referred for a hemotological opinion.

Her primary complaint continued to be fatigue. She denied anorexia, weight loss, abdominal discomfort, diarrhea or steatorrhea. Past medical history was significant for iron replacement therapy that she required during her two pregnancies in 1978 and 1981. There was no family history of hematological or gastrointestinal disorders. Her only medication was ferrous sulfate. Physical examination was normal.

Initial investigations revealed a hemoglobin of 111 g/L, mean corpuscular volume of 100 fL, white blood cell count of 5.0 × 10 /L with a normal differential and platelet count of 241 × 10 /L. Red cell morphology was abnormal with marked anisocytosis, acanthocytosis, target cells and Howell-Jolly bodies being present. Serum ferritin (7 μ g/L) and red cell folate (105 nmol/L) were reduced. Serum vitamin B_{12} was normal. Serum levels of urea nitrogen, electrolytes, creatinine, albumin, total protein, calcium, SGOT, SGPT and bilirubin were normal. A bone marrow aspirate showed absent hemosiderin with macronormoblastic erythropoiesis. The presence of nutritional anemia (iron and folate deficiency) with evidence of hyposplenism led us to perform a biopsy of the duodenal mucosa. Villous atrophy was found confirming the diagnosis of gluten-sensitive enteropathy and she was started on a gluten-free diet.

DISCUSSION

Gluten-sensitive enteropathy (nontropical sprue) is a disorder in which the villi of the small bowel atrophy, leading to malabsorption. The pathogenesis of the condition is believed to relate to a hyper-sensivity reaction to glutens in the diet. Affected patients frequently manifest anorexia, weight loss, abdominal bloating, diarrhea and steatorrhea. Symptoms relating to malabsorption of calcium (tetany, bone disease), fat-soluble vitamins (bone disease, coagulopathy, night blindness, myelopathy) and iron or folate (fatigue, glossitis) also commonly occur. Nevertheless it is quite clear that a spectrum of disease exists. Those with classic symptoms of diarrhea, weight loss, steatorrhea and malnutrition are usually diagnosed in childhood. Patients with more subtle symptomatology may be more common and can escape diagnosis until well into adult life.[1]

In symptomatic individuals, serum proteins, calcium and magnesium are reduced but these values may be normal in less symptomatic forms of the disease. Stool fat excretion is abnormal in up to two-thirds of all cases of nontropical sprue.[1] Serum carotene levels are usually reduced even if the stool fat excretion is normal.[1] D-xylose absorption test is abmormal in most patients (90%).[1] Radiological abnormalities are almost always present although frequently non-specific.[1]

Our first patient presented for urological investigations with an incidental anemia and, aside from recent onset of anorexia, she had no gastrointestinal symptoms. The presence of normal values for serum proteins, calcium, vitamin B_{12} and carotene did not suggest gastrointestinal malabsorption. A combined deficiency of iron and folate was present and was suspected on the basis of a high red cell distribution width, suggesting a dimorphic population of red cells. The second patient had a more chronic anemia and at the time of tertiary referral had been noted to be both iron and folate deficient in the past. Nevertheless, she denied any gastrointestinal disturbance and the presence of normal values for serum proteins, calcium, vitamin B_{12} and carotene did not suggest gastrointestinal malabsorption. As in the first patient, a combined iron and folate deficiency was suggested by a high red cell distribution width consistent with a dimorphic population of red cells.

In both cases, morphologic evidence of hyposplenism on peripheral blood film was present and was diagnostically important. The presence of acanthocytes, Howell-Jolly bodies and target cells were classical for hyposplenism. The strong association between functional hyposplenism, nutritional anemia and coeliac disease led us to further investigations of the rewarding diagnosis of gluten-sensitive enteropathy. The occurrence of hyposplenism in malabsorption syndromes was first described in 1923 by Blumgart[8] but specific studies of the frequency of hyposplenism in nontropical sprue were not performed until McCarthy studied twenty-five patients and found peripheral blood smear evidence of hyposplenism in 16%.[4] Subsequent studies based on blood smears only established the frequency of hyposplenism in gluten-sensitive enteropathy at 28 to 36%.[4-7]

The incidence of hyposplenism in nontropical sprue is dependant on the method of evaluation of splenic function. A necropsy study found that 44% of patients had pathological splenic atrophy.[9] Using pitted red cell analysis, a sensitive technique for evaluation splenic function, O'Grady clearly defined the relationship between gluten-sensitive enteropathy and hyposplenism.[3] By pitted red cell analysis, 76.2% of patients with gluten-sensitive enteropathy were hyposplenic. Further-

more, the more severe the small bowel mucosal atrophy, the more likely one is to find defective splenic function. Hyposplenism occurs only in adults with coeliac disease and fluctuates with the activity of the disease.[8,10] Evidence of hyposplenism usually resolves with institution of a gluten-free diet. Those that do not resolve (10%) are presumed to have permanent splenic atrophy.[7]

The two patients reported here had abnormal red cells morphology in keeping with hyposplenism. Neither had gastrointestinal symptoms suggestive of nontropical sprue but were undergoing evaluation for anemia. We suggested that regardless of symptomatology, patients with anemia and red cell morphology suggestive of defective splenic function (target cells, acanthocytes and Howell-Jolly bodies on peripheral smear) should be investigated for occult nontropical sprue. Furthermore, since screening laboratory tests for gastrointestinal malabsorption may be normal, duodenoscopy with small bowel biopsy is mandatory. Commencement of a gluten-free diet in these "asymptomatic" patients frequently leads to a distinct improvement in nutritional state and general health. □

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Obituary

Dr. Gabriel C. Boudreau, (82) of Cheticamp, Nova Scotia died on April 11, 1990. Born in Cheticamp he received his medical degree from Dalhousie Medical School in 1935 and practised medicine in Cheticamp until his retirement in 1974. He then devoted his retirement years to farming. He is survived by a son, and a daughter, to whom the *Journal* extends sincere sympathy.

POSTPARTUM PSYCHIATRIC DISORDERS IN NOVA SCOTIA

Continued from page 100.

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No one could have foreseen the speed and scale with which advances in medicine and public health would create a problem of overpopulation that threatens to undo much of what medical science has worked for. Thirty years ago the talk was all of how people of the Western world were reproducing themselves too slowly to make good the wastage of mortality; we heard tell of a "Twilight of Parenthood", and wondered rather fearfully where it would all end.

Sir Peter Medawar (1915-1987)

Current Topics in Community Health

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THE CASE FOR NEEDLE EXCHANGE PROGRAMS

On April 21, 1990, the Nova Scotia Department of Health and Fitness reported a possible outbreak of HIV infection among injection drug users who shared needles.[1] This brought calls for a government-sponsored needle exchange program; calls which were soundly rejected by the health minister.[2,3] The Federal Government provides 50% funding for intervention programs for injection drug use and 100% funding for evaluation of these programs.[4] Programs operate in Montreal, Vancouver and Toronto under this funding formula. It is unknown how many community-funded needle exchange programs there are in Canada. One such program is run by the Nova Scotia Persons with AIDS Coalition in Halifax.

The case in favour of needle exchange programs is impressive. Injection drug users (IDU) are the second largest risk group for AIDS; they are also the pivotal link between heterosexual transmission and vertical transmission to children infected *in utero* or shortly after birth. The main conduit of HIV transmission among drug users is through the sharing of needles.

Spread by needle sharing is very effective due to the transfusion of infected blood and introduction of a contaminated needle directly into a vein or subcutaneous site. Several factors seem to enhance this process further, including the number of partners shared with, the frequency of injecting, and the use of intravenous cocaine.[5] The withdrawal state often leads to indiscriminate sharing.[6] For these reasons, once introduced into the IDU community, HIV can spread very rapidly.[7-9]

Almost all IDU share at some time. There are several reasons for this: access to readily available and affordable "works" may be limited; possession of drug-related paraphernalia is illegal in some areas; and needle sharing has social and ritual appeal for some users.[5,6]

IDU are not ignorant about AIDS; they know it is transmitted through sharing needles and they know that using clean needles can prevent it.[10] Many have modified their needle sharing behaviour and many engage in safer sexual practices.[6,10] Numerous studies indicate that injection drug users are knowledgeable about AIDS, its manner of transmission, its common symptoms; but few know how to sterilize injection equipment.[6,11,12]

A non-judgemental approach which provides risk-reducing options, facilitates entry into treatment for substance abuse and encourages both safer injection and sexual practices, is best to stem the spread of HIV in the IDU population. Of particular note among such endeavours are the multi-faceted needle exchange programs.[5]

Most needle exchange programs have a "knowledge and means" approach, wherein the target group is educated about the epidemiology of HIV and ways in which its spread can be stopped, and then supplied with the means (in this case, syringes and condoms) to effect the recommended changes.[5] The Junkiebond introduced the idea of needle exchange in 1984 in Holland for the prevention of hepatitis B in IDU.[13] Other programs were established in the mid-1980s in the United Kingdom, Australia and Sweden in response to the AIDS epidemic. These programs have achieved small but notable successes in reducing high-risk injection practices and risky sexual behaviour and increasing the demand for addiction therapy without the feared overall increases in injection drug use.[6,13]

In San Francisco, community health outreach workers are distributing small bottles of bleach and instructions for cleaning injection equipment. Prior to the program, three percent of IDU used bleach for this purpose; a year later 67% reported that they did so.[14]

The Vancouver Experience

In February 1989, Vancouver City Council approved a needle exchange program proposal for a 10 month trial with $100,000 funding in the form of a grant to a local agency, the Downtown Eastside Youth Activities Society. The Vancouver Health Unit was assigned the responsibility of overseeing the operation of the program, providing the needed supply of syringes and condoms, and affording professional input and guidance. Two mature and street-wise workers were hired and underwent two weeks of training.[5]

The program's philosophy and approach stressed confidentiality and unobtrusiveness. Only two "rigs" were given out at a time and track marks were checked before needles were dispensed to verify previous drug use. From its initial fixed office site, the program moved into other areas — setting up a table in the Granville Mall, doing walkabout tours of high risk areas and dispensing needles, condoms and "bad trick lists", using a van. Besides needle exchange, the program offered educational materials and advice on HIV and condoms. After numerous requests for medical services were made, a medical clinic was set up near the exchange site. Referrals to other community agencies were arranged through a large resource network.

During the trial period, the program encountered some problems with public opposition; it had to answer

claims that more needles were being discarded in the streets; security of the fixed site was a major concern after two break-ins; clients of the program soon demanded different size needles and syringes for different drug combinations and complained about the taste of nonoxynol-containing condoms which they used for oral sex; and soon after inception, the program's budget was exceeded because demand outstripped supplies. There was no increase in the commencement of injection drug use by youth, instead there was a great increase in requests for referral to addiction services (which were lacking).

In concluding their evaluation report, program operators wrote:

"The needle exchange program continues to perform far beyond our original expectations. Not only are the real number of people registered in the program increasing, but also the responsibleness of their behaviour is keeping pace, as evidenced by the ever-increasing rate of exchange, number of regular users and requests for medical and addiction treatment. As we learn more about our clients and the various areas where they hang out, we are able to offer services more appropriate to them. With our outreach services, particularly with the van, we seem to be capturing a sub-population not reached before. In addition, as the program gets better known and trusted by the clients and community agencies, we are getting ever-increasing requests for a wide variety of services. Of particular note, since our ultimate ideal is to get people off intravenous drugs entirely, are the requests for addiction treatment".[5]

Public health efforts to prevent AIDS among injection drug users are made difficult by the characteristics of the IDU subculture, particularly its mistrust and contempt for authority.[6] Efforts to encourage subculture change towards safe needle use and safer sexual practices are more likely to be effective if they are carried out within the context of a street-smart, non-judgemental needle exchange program which offers IDU the ways and means of preventing HIV infection. □

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Notice Board

Physicians will be generally aware of the identification of the cystic fibrosis gene by the Toronto genetics team headed by Dr. Tsui and they may have speculated as to how this discovery will influence medical care. In this regard, the American Society of Human Genetics has issued the following statement (abridged):

> The recent identification of the gene associated with cystic fibrosis offers great hope for new treatments for this common disease. Even more immediately, it is now possible to identify healthy individuals who carry the CF trait. However, the current test detects only 70% of carriers, and there is little experience in the delivery of such complex information to large populations. Accordingly, there are serious reservations and there is no consensus amongst genticists regarding wide-spread screening for CF carriers at this time.
>
> However, *carrier testing should be offered to couples in which either partner has a close relative affected with CF.*
>
> While it is recognized that testing of highly motivated individuals in the general population may occur, it is the position of the American Society of Human Genetics that *routine CF carrier testing of pregnant women and other individuals is NOT yet the standard of care in medical practice.* [our italics].

With appropriate genetic counselling, testing of appropriate individuals and families for the presence of the CF gene has already begun in the Maritimes, through the facilities of the Molecular Diagnostics Laboratory at the IWK Children's Hospital.

Physicians caring for other CF families may contact Dr. C.T. Gillespie (IWK: 428-8219), Dr. R. Michael (VGH: 422-1708), or Dr. D.E.C. Cole (IWK: 428-8321) for further information concerning carrier testing in such families. □

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