

Hemoglobinopathies: how big a problem?

Over the last few centuries, but especially since World War II, there has been continuing emigration from Africa, Asia and Europe to North America. As a result hemoglobinopathies are now recognized as the most important group of genetic diseases in the United States. Few can doubt that hemoglobinopathies present a health-care problem in Canada also, but the size of the problem is much more difficult to estimate. With a knowledge of the countries where the abnormal hemoglobins and thalassemia originate and a copy of the Canadian census and immigration figures, one would expect to be able to predict the impact of hemoglobinopathies on present-day Canada. There are a number of drawbacks to this "armchair" approach but, because it may be followed by the planners of health-care delivery, it is at least worthy of exploration.

The geographic areas where the common abnormal hemoglobins (sickle cell, C, D Punjab [or Los Angeles] and E) are endemic are well recognized.^{1,2} Hemoglobin C is localized to persons of West African origin. In contrast, sickle cell hemoglobin is more widespread; it is found predominately in African blacks, but also to a lesser extent in persons from Greece and the Middle East and among aboriginal tribes in India. Hemoglobin D Punjab and E are likely to be seen in persons of Asiatic origin; the former is found mainly in the Punjab and the latter in Thailand, among the native Indo-Chinese rather than the more recently arrived Chinese.

Beta-thalassemia, although first recognized by Cooley and Lee³ in Italian immigrants in the United States and therefore named Mediterranean anemia, exists widely across the Mediterranean and the Middle and Far East. Despite the claim that

there is a higher frequency of thalassemia in the Chinese than in the total Mediterranean population,⁴ it is interesting that the 966 persons with thalassemia variants found in the Vancouver survey of Gray and Marion (see page 701 for their report) were reasonably evenly divided between Mediterranean and Asian origin.

It is convenient to consider that α - and β -thalassemia have roughly the same geographic distribution.⁵ However, the carrier state of α -thalassemia is symptomless and is therefore difficult to categorically detect without support from a direct, but somewhat complicated, measurement of α -chain production in the erythrocytes. Carriers of α -thalassemia are the exception to the rule in that their condition may be suspected when an unusually low mean corpuscular volume is recorded on an electronic cell counter.⁶ A more severe form of α -thalassemia, hemoglobin H disease, presents with moderately severe anemia and splenomegaly, and again appears to have roughly the same distribution as β -thalassemia. Alpha-thalassemia major, which is incompatible with life, is especially prevalent in Asia; it is the most frequent cause of hydrops fetalis in Malaysia.⁷

Among the hemoglobinopathies, sickle cell anemia and β -thalassemia major, because of their frequency and clinical severity, are the most important in Canada. With a carrier rate of about 8% for the sickle cell trait among blacks in the United States one could expect about 1 in 500 blacks in Canada to be born with this potentially lethal disease. Sickle cell anemia (homozygous sickle cell disease) presents clinically with either the classic painful infarctive crisis or a catastrophic decrease in the steady state concentration of hemoglobin.

Beta-thalassemia minor (the carrier state of β -thalassemia) may be found in 5% to 10% of many of the affected populations. It presents classically as iron-resistant hypochromic anemia, with a hemoglobin concentration of 10 to 12 g/dL. Because of the superfluity of erythrocytes, an automated counter gives lower values for the mean corpuscular hemoglobin and the mean corpuscular volume than one would expect in pure iron deficiency. The patient with β -thalassemia minor commonly has normal or increased stores of iron. Despite the fact that the coexistence of β -thalassemia and iron deficiency is perhaps more common than previously realized, iron therapy should not be given unless a decrease in the serum concentration of iron is first demonstrated. Beta-thalassemia major, with its severe anemia and massive hepatosplenomegaly, presents a heavy therapeutic challenge but is seldom a diagnostic problem; even if the physician is uncertain about the diagnosis, the disease is all too often recognized by the relatives of the afflicted child.

The Canadian population can be divided relatively easily into three categories with the use of the census and immigration figures.⁸

1. *Native:* By sheer weight of numbers Canada has an immigrant population. The native population (about 300 000) do not have hemoglobinopathies to add to what many consider an already heavy burden of disadvantage.

2. *British and French:* Between 1871 and 1971 the Canadian population increased from 3 689 000 to 21 568 000. The most pronounced changes during this period were the decrease in the proportion of British origin (from more than 60% in 1871 to 45% by 1971) and the increase in the proportion of those of all

origins other than French (from less than 10% in 1871 to more than 25% by 1971). The proportion of French origin remained relatively constant (at about 30%).

Although not major carriers of hemoglobinopathies, the native British population may be expected to carry hemoglobin D Punjab with a frequency of about 0.1% — a legacy of the substantial presence of the British military in the Indian subcontinent for 200 years.⁹ Again, as Desjardins and colleagues point out in this issue of the Journal (page 709), one is not surprised to find that Mediterranean anemia occurs to a greater or lesser extent in a Canadian population of French origin.

3. *All others*: It is unfortunate, from the point of view of this review, that inexactness within the census figures is likely to arise at the subdivision of this heterogeneous label. For example, the rapid increase in the last decade in the "British" population (perhaps at the expense of "all others") may be in part due to the fact that "English" was the first choice as an answer to question 15 of the 1971 Census of Canada — "To what ethnic or cultural group did you or your ancestor (on the male side) belong on coming to this continent?" With such reservations in mind, one learns that there was an increase in Canada from 1961 to 1971 of 60 600 in the number of Chinese and 61 200 in the number of East Indians; the total number of "Asians" in 1971 was 285 500. The increase in the number of blacks in the same period, 2300, might appear modest to those living in the larger cities of Canada. Kralt believes that the estimate of 34 400 blacks in Canada in 1971 is probably conservative (personal communication, 1978). However, one might expect a considerable number of West Indians (whose total number was 28 000 in 1971) to fall into this category.

Canadian immigration figures based on the country of last permanent residence (i.e., of 1 year or more) give more recent data.^{10,11} For example, the annual number of persons from the West Indies immigrating to Canada increased steadily from 1941 (118) to 1974 (23 670), then declined in 1975 (17 800), 1976 (14 700) and the first quarter of 1977 (2554). The figures from Asia have followed the same trend, increasing

from 1941 (307) to 1974 (50 566), then declining in 1975 (47 382), 1976 (44 328) and the first quarter of 1977 (7027).

Most of the carriers of β -thalassemia of "Mediterranean" origin detected in the survey of Gray and Marion were Italians and Greeks. The pattern of immigration of these groups since World War II has been the same as that of the West Indians and Asians. However, the peak years were 1966 for the Italians (31 625) and 1967 for Greeks (10 650).

Figures such as these have to be interpreted with caution. For example, on the sole basis of country of last permanent residence, it must follow that not all "British" persons are native Britons. Indeed, the difficulties in compiling these data may be illustrated by my experience. Although I was born in Asia, my family and I were the only Caucasians among the band of hopeful "British" undergoing immigration screening one morning at the Canadian Consulate in Birmingham, England.

Assuming reasonable accuracy of the total immigration figures, a further problem in assessing health care needs arises because of the provincial disparity in the settlement pattern of different ethnic groups. As well as recognized historical patterns, such as the early black settlements in Nova Scotia,^{12,13} there are more recent inequalities based on the general preference of many newly arrived immigrants to live in an urban area rather than a rural area. Because of such patterns a screening program for the detection of hemoglobinopathies in an urban area of British Columbia would have little relevance in a rural area of Newfoundland.

By now it must be apparent that the available population data are unlikely to be particularly helpful in the planning of Canadian health care programs directed at detection and treatment of hemoglobinopathies. Unfortunately, there appears to be no substitute for studies such as those reported in this issue of the Journal and those conducted by Ali¹⁴ in Ontario and Vella¹⁵ in Saskatchewan. With such studies the demand for therapy (mainly for sickle cell disease and β -thalassemia major) can be logically assessed on both a national and a provincial basis. In addition, one can be prepared, when requested,

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INDICATIONS: For management of anxiety, tension, fear, agitation, irritability, insomnia and anxiety associated with depression, e.g. as in transient situational disorder, psychoneurotic reaction, psychophysiological reaction, geriatric behavioral disturbances or personality disorder. Also in anxiety syndrome secondary to organic disease and in residual anxiety syndrome in alcoholics and in alcohol withdrawal.

CONTRAINDICATIONS: Not indicated in children under 6 years of age. No definite established dose for children 6 to 12 years of age. Contraindicated in patients who have exhibited previous hypersensitivity to oxazepam. Not indicated in psychoses.

PRECAUTIONS: Ambulatory patients may become drowsy or dizzy or experience reduced tolerance to alcohol, so should be warned against driving automobiles or operating dangerous machinery. Some cases of attempted suicide have been reported in which highest dosage ingested was in excess of 600 mg. When treatment is protracted periodic blood counts and liver function tests may be advisable. If rash or other symptoms of hypersensitivity occur, administration of oxazepam should be discontinued and appropriate symptomatic treatment initiated. Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. Withdrawal symptoms upon discontinuation have been noted in some patients exhibiting drug dependence through chronic overdose. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive, prolonged use in susceptible patients (alcoholics, addicts) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Withdrawal symptoms following abrupt discontinuances are similar to those seen with barbiturates.

Safety for use in pregnant women has not been established, therefore oxazepam should not be used during the first trimester of pregnancy unless the benefit to the patient outweighs the possible hazards to the fetus.

ADVERSE EFFECTS: Rarely require discontinuance of therapy. Transient mild drowsiness occurs during initial days — if it persists, reduce dosage. In a few cases, dizziness, vertigo, headache and rarely syncope have also occurred. Mild paradoxical reactions, e.g. excitement, stimulation of affect have occurred in psychiatric patients, usually in first 2 weeks of therapy. Minor diffuse skin rashes, leukopenia, hepatic dysfunction including jaundice and nausea, edema, slurred speech, tremor, altered libido and lethargy have occurred infrequently. Ataxia has been reported in rare instances.

DOSAGE: Mild to moderate anxiety syndromes, 10 to 15 mg 3 or 4 times daily. Severe anxiety syndromes, 15 to 30 mg 3 or 4 times daily. Geriatric behavior problems, 10 mg initially 3 times a day, if necessary increase cautiously to 15 mg 3 or 4 times daily. Residual anxiety syndrome in alcoholics and in alcohol withdrawal, 15 to 30 mg 3 or 4 times daily.

SUPPLIED: Each scored tablet contains: oxazepam 10 mg (light yellow), 15 mg (yellow) or 30 mg (white). Tablet weight: 190 mg. Caloric contents: 0.5 cal. tablet. Bottles of 100 and 500 tablets.

REFERENCES: 1. Greenblatt, D.J., Shader, R.I., Koch-Weser, J.: Pharmacokinetics In Clinical Medicine: Oxazepam Versus Other Benzodiazepines, Disease of the Nervous System, 36:5:2:6-13, May, 1975. 2. Bianchi, G.N., The Rational Use of Anxiolytics, New Zealand Medical Journal, 83:563, 303-308, May, 1976. 3. Ayd, F.J., Oxazepam: An Overview. Diseases of the Nervous System, 36:5:2:14-16, May, 1975. 4. Merles, S., Koepke, H.H.: The Use of Oxazepam in Elderly Patients, Diseases of the Nervous System 36:5:2: 27-29, May, 1975. 5. Shull, H.J., Jr., Wilkinson, G.R., Johnson, R., Schenker, S.: Normal Disposition of Oxazepam in Acute Viral Hepatitis and Cirrhosis. Annals of Internal Medicine, 84:420-425, 1976. 6. Greenblatt, D.J., Shader, R.I.: Drug Therapy: Benzodiazepines. New England Journal of Medicine, 291: 1011-1015, 1239-1243, 1974.



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ADULT DOSAGE: Hypertension: Starting dosage is one tablet twice daily after meals. Dosage can be subsequently increased or decreased according to patient's need. If two or more tablets per day are needed, they should be given in divided doses. Edema: Starting dosage is one tablet twice daily after meals. When dry weight is reached, the patient may be maintained on one tablet daily. Maximum dosage four tablets daily.

INDICATIONS: Mild to moderate hypertension in patients who have developed hypokalemia and in patients in whom potassium depletion is considered especially dangerous (e.g. digitalized patients). Medical opinion is not unanimous regarding the incidence and/or clinical significance of hypokalemia occurring among hypertensive patients treated with thiazide-like diuretics alone, and concerning the use of potassium-sparing combinations as routine therapy in hypertension.

Edema of congestive heart failure, cirrhosis, nephrotic syndrome, steroid-induced edema and idiopathic edema. 'Dyazide' is useful in edematous patients whose response to other diuretics is inadequate.

CONTRAINDICATIONS: Progressive renal dysfunction (including increasing oliguria and azotemia) or increasing hepatic dysfunction. Hypersensitivity. Elevated serum potassium. Nursing mothers.

WARNINGS: Do not use potassium supplementation or other potassium-conserving agents with 'Dyazide' since hyperkalemia may result. Hyperkalemia (>5.4 mEq/l) has been reported ranging in incidence from 4% in patients less than 60 years of age to 12% in patients 60 and older, with an overall incidence of less than 8%. Rare cases have been associated with cardiac irregularities. Make periodic serum potassium determinations, particularly in the elderly, in diabetics, and in suspected or confirmed renal insufficiency. If hyperkalemia develops, withdraw 'Dyazide' and substitute a thiazide alone.

Hypokalemia is less common than with thiazides alone, but if it occurs it may precipitate digitalis intoxication.

PRECAUTIONS: Check laboratory data (e.g. BUN, serum electrolytes) and ECG's periodically, especially in the elderly, in diabetics, in renal insufficiency, and in those who have developed hyperkalemia on 'Dyazide' previously. Electrolyte imbalance may occur, especially where salt-restricted diets or prolonged high-dose therapy is used. Observe acutely ill cirrhotic patients for early signs of impending coma. Reversible nitrogen retention may be seen. Observe patients regularly for blood dyscrasias, liver damage or other idiosyncratic reactions; perform appropriate laboratory studies as required. Sensitivity reactions may occur, particularly in patients with history of allergy or bronchial asthma. Periodic blood studies are recommended in cirrhotics with splenomegaly. Adjust dosage of other antihypertensive agents given concomitantly. Antihypertensive effects of 'Dyazide' may be enhanced in the post-sympathectomy patient. Hyperglycemia and glycosuria may occur. Insulin requirement may be altered in diabetics. Hyperuricemia and gout may occur. Thiazides have been reported to exacerbate or activate systemic lupus erythematosus. Pathological changes in the parathyroid glands have been reported with prolonged thiazide therapy. Triamterene may cause a decreasing alkali reserve, with the possibility of metabolic acidosis. Serum transaminase elevations sometimes occur with 'Dyazide'. Thiazides can decrease arterial responsiveness to norepinephrine and increase tubocurarine's paralyzing effect; exercise caution in patients undergoing surgery. Thiazides cross the placental barrier and appear in breast milk; this may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possible other adverse reactions that have occurred in the adult. Use in pregnancy only when deemed necessary for the patient's welfare.

ADVERSE REACTIONS: The following adverse reactions have been associated with the use of thiazide diuretics or triamterene: Gastrointestinal: dry mouth, anorexia, gastric irritation, nausea, vomiting, diarrhea, constipation, jaundice (intra-hepatic cholestatic) pancreatitis, sialadenitis. Nausea can usually be prevented by giving the drug after meals. It should be noted that symptoms of nausea and vomiting can also be indicative of electrolyte imbalance (See Precautions).

Central nervous system: dizziness, vertigo, paresthesias, headache, xanthopsia. Dermatologic — Hypersensitivity: fever, purpura, anaphylaxis, photosensitivity, rash, urticaria, necrotizing angitis. Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Cardiovascular: orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. Electrolyte imbalance (See Precautions). Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

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to offer the carriers of sickle cell hemoglobin and β -thalassemia minor the necessary facilities for genetic counselling.

The Canadian Sickle Cell Society is seeking support for a large-scale screening program among the black population of Canada. Many of the errors made in the massive sickle cell program in the United States, when enthusiasm appeared at times to overtake wisdom, should be preventable in Canada. Nevertheless, despite the advantages offered by a late start and a slower pace, it would be something of a miracle if this country succeeded in travelling such a pot-holed road unscathed.

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References

- LIVINGSTONE FB: *Abnormal Hemoglobins in Human Populations*, Aldine, Chicago, 1967
- Idem: *Data on the Abnormal Hemoglobins and Glucose-6-Phosphate Dehydrogenase Deficiency in Human Populations*, tech rep no 3, Museum of Anthropology, U of Mich Pr, Ann Arbor, 1973
- COOLEY TB, LEE P: A series of cases of splenomegaly in children with anemia and peculiar bone changes. *Trans Am Pediatr Soc* 37: 29, 1925
- LEHMANN H, HUNTSMAN RG: *Man's Haemoglobins; Including the Hemoglobinopathies and Their Investigation*, North-Holland, Amsterdam, 1974, p 313
- WEATHERALL DJ, CLEGG JB: *The Thalassaemia Syndromes*, 2nd ed, Blackwell Sci Pub, Oxford, 1972
- HUISMAN AJ, JONXIS JHP: General survey and history, in *The Hemoglobinopathies: Techniques of Identification (Clinical and Biochemical Analysis)*, Dekker, New York, 1977, p 55
- HUNTSMAN RG, JENKINS GC: Blood diseases in the tropics, in *Tropical Pathology* (Spezialie Pathologische Anatomie Series special edition: vol 8), SPENCER H, et al (eds), Springer Verlag, New York, 1973
- KRALT J: Profile studies. Demographic, cultural and economic aspects of ethnic origins of Canadians, in *1971 Census of Canada*, vol 5, part I, cat no 99-709, census division, Statistics Canada, Ottawa, May 1977
- KONIGSBERG W, HUNTSMAN RG, WADIA F, et al: Haemoglobin D β Punjab in an East Anglian family. *J R Anthropol Inst* 95: 295, 1965
- Statistics Canada: Historical summary, 1970. *Can Stat Rev* (special ed): 8, 1972 (cat no 11-505)
- Idem: Immigration to Canada by country of last permanent residence. *Can Stat Rev* 43 (2): 14, 1978 (cat no 11-003E)
- NORTON S, MAXWELL I: Sickle cell survey in Halifax county: a pilot study. *NS Med Bull* 53: 108, 1974 1974
- ROBINSON C: Exile, in *The Fighting Maroons of Jamaica*, Collins and Sangster, Kingston, Jamaica, 1969, pp 143-54
- ALI MAM: Hemoglobinopathies in the Hamilton region. I. A 4-year survey. *Can Med Assoc J* 112: 698, 1975
- VELLA F: The human hemoglobin variants in Canada. *Clin Biochem* 8: 341, 1975

BOOKS

This list is an acknowledgement of books received. It does not preclude review at a later date.

ALCOHOLISM AND TREATMENT. David J. Armor, J. Michael Plich and Harriet B. Stambul. 349 pp. Illust. John Wiley & Sons, Inc., Somerset, 1978. \$16.95. ISBN 0-471-02558-5

AND A TIME TO LIVE. Toward Emotional Well-Being During the Crisis of Cancer. Robert Chernin Cantor. 280 pp. Harper & Row, Publishers, New York; Fitzhenry and Whiteside, Don Mills, 1978. \$12.50. ISBN 0-06-010623-9

BAILEY'S TEXTBOOK OF HISTOLOGY. 17th ed. Wilfred M. Copenhaver, Douglas E. Kelly and Richard L. Wood. 800 pp. Illust. The Williams & Wilkins Company, Baltimore; Burns & MacEachern Limited, Don Mills, 1978. \$31.20. ISBN 0-683-02078-1

THE CARDIAC ARRHYTHMIAS. 3rd ed. Brendan Phibbs and Gordon A. Ewy. 241 pp. Illust. The C.V. Mosby Company, Saint Louis, 1978. \$14.25, paperbound. ISBN 0-8016-3911-5

ELECTRODIAGNOSIS OF NEUROMUSCULAR DISEASES. 2nd ed. Joseph Goodgold and Arthur Eberstein. 281 pp. Illust. The Williams & Wilkins Company, Baltimore; Burns & MacEachern Limited, Don Mills, 1978. \$23.95. ISBN 0-0683-3685-8

MEDICAL PHARMACOLOGY. Principles and Concepts. 9th ed. Edited by Andres Goth and Parkhurst Allan Shore. 766 pp. Illust. The C.V. Mosby Company, Saint Louis, 1978. \$22.75. ISBN 0-8016-1948-3

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