3. Lipman J, Wing J. The adult respiratory distress syndrome: a review, some thoughts and a few new ideas. *S Afr Med J* 1981; **59:** 779-782.
4. Lipman J, Roos CP, Plit M *et al.* The correlation between cardiac output and mixed venous oxygen tensions. *S Afr Med J* 1982; **62:** 611-613.
5. Martin WE, Cheung PW, Johnson CC, Wong KC. Continuous monitoring of mixed venous oxygen saturation in man. *Anesth Analg* 1973; **52:** 784-793.
6. Moxham J, Armstrong RF. Continuous monitoring of right atrial oxygen tensions in patients with myocardial infarction. *Intensive Care Med* 1981; **7:** 157-164.
7. Goldman RH, Klughaupt M, Metcalf T, Spivack AF, Harrison DC. Measurement of central venous oxygen saturations in patients with myocardial infarcts. *Circulation* 1968; **38:** 941-946.
8. Hurewitz A, Bergofsky EH. Adult respiratory distress syndrome. *Med Clin North Am* 1981; **65:** 33-51.
9. Hutter AM, Moss AJ. Central venous oxygen saturations: value of serial determination in patients with acute myocardial infarcts. *JAMA* 1970; **212:** 299-303.
10. Stanley TH, Isern-Amaral J. Periodic analysis of mixed venous oxygen tension to monitor the adequacy of perfusion during and after cardiopulmonary bypass. *Can Anaesth Soc J* 1974; **21:** 454-460.
11. Kosanin R, Stein ED, Stein JM. Shunt fractions obtained via catheterization of the pulmonary artery and the superior venae cavae. *Anesth Rev* 1980; **7:** 29-32.
12. Krauss H, Verdouw PD, Hugenholtz PG, Nanta J. Online monitoring of mixed venous oxygen saturations after cardiothoracic surgery. *Thorax* 1975; **30:** 636-643.
13. Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturations in shock: a study in man. *Anesthesiology* 1972; **36:** 472-478.
14. Tahvanainen J, Meretoja O, Nikki P. Can central venous blood replace mixed venous blood samples? *Crit Care Med* 1982; **10:** 758-761.
15. Fahey PJ, Harris K, Vanderwarf C. Clinical experience with continuous monitoring of mixed venous oxygen saturation in respiratory failure. *Chest* 1984; **86:** 748-752.
16. Birman H, Haq A, Hew E, Aberman A. Continuous monitoring of mixed venous oxygen saturation in hemodynamically unstable patients. *Chest* 1984; **86:** 753-756.
17. Gore JM, Sloan K. Use of continuous monitoring of mixed venous saturation in the coronary care unit. *Chest* 1984; **86:** 757-761.
18. Walls EW. The blood vascular and lymphatic systems. In: Romanes GJ, ed. *Cunningham's Textbook of Anatomy.* 11th ed. London: Oxford University Press, 1978: 845.
19. Guyton AC. The coronary circulation. In: *Textbook of Medical Physiology.* 4th ed. Philadelphia: WB Saunders, 1971: 359.
20. Civetta JM. Invasive catheterization. In: Shoemaker WC, Leigh Thompson WL, eds. *Critical Care: State of the Art.* Vol. I. (B). Fullerton, Calif.: Society of Critical Care Medicine, 1980: 8, 33.
21. Editorial. Complications of pulmonary artery balloon flotation catheters. *Lancet* 1983; **i:** 37-38.
22. Scheinman MM, Brown MA, Rapaport E. Critical assessment of the rise of central venous oxygen saturations as a mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation* 1969; **30:** 165-172.
23. Barrett-Boyes BG, Wood EH. The oxygen saturations in blood venae cavae, right heart chambers and pulmonary vessels in healthy subjects. *J Lab Clin Med* 1957; **50:** 93-106.
24. MacDonald R. Red cell 2,3 diphosphoglycerate and oxygen affinity. *Anaesthesia* 1977; **32:** 544-553.
25. Kasnitz P, Druger GL, Yorra F, Simmons DH. Mixed venous oxygen tension and hyperlactatemia. *JAMA* 1976; **236:** 570-574.
26. Suter PM, Lindauer JM, Fairley HB, Schlobohm RM. Errors in data derived from pulmonary artery blood gas analysis. *Crit Care Med* 1975; **3:** 175-181.

Progressive familial heart block

Part I. Extent of the disease

MARIE TORRINGTON, H. W. WEYMAR, P.-L. VAN DER MERWE, A. J. BRINK

Summary

Progressive familial heart block (type I) has been identified in the RSA. Since 1977 many families have been referred for pedigree tracing. The present probands of some 9 pedigrees are the descendants of specific children of an immigrant; other genetic diseases appear in these pedigrees. The necessity of identifying, diagnosing and possibly treating the descendants of carriers is emphasized.

S Afr Med J 1986; **70:** 353-355.

Since 1977, when progressive familial heart block (PFHB) was identified in the RSA,[1] a further 40 families have been referred for investigation and identification of this disease. The probands requested the investigation of their family histories because they were aware of sudden deaths in the families, because the death had occurred at a comparatively young age, and because their observation had led to anxiety.

Investigation of these family pedigrees sought to identify new branches of families with PFHB, which could have had a link with the original study.[1] It also sought to establish a possible connection between PFHB and other genetic diseases, to document the progression of heart blocks in the identified individuals (Part II of this study; p. 356), and finally to offer counselling and referral to the affected members of the families whenever necessary.

Institute of Biostatistics of the South African Medical Research Council, and Cardiac Unit, Departments of Internal Medicine and Paediatrics, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP
MARIE TORRINGTON, D.PHIL.
H. W. WEYMAR, R.C.T. (CARDIOLOGY)
P.-L. VAN DER MERWE, M.B. CH.B., M.MED., F.C.P. (S.A.)
A. J. BRINK, M.D., F.R.C.P., D.SC.

Patients and methods

South Africa is fortunate in that it has unique documentation on all the immigrants who came to this country in the 17th century. This documentation, classified in the work of De Villiers and Pama[2] and the Dutch Reformed Church records, makes it possible to trace white South African families from the present generation back to the original European immigrants. Such families, at the rate of a new generation every 25 years, can have only 13 generations. Present knowledge of a hereditary disease spread over current generations therefore allows researchers to seek a founder member in the original ancestors. Such work is, however, time-consuming and this article refers to only 9 families in whom full documentation was possible.

Results

Families V, W, R, F, VN

These families were traced back to the same ancestors of D and F as described by Brink and Torrington,[1] namely individuals 3, 4

and 5 — generation 1 — in Fig. 1. In generations 6, 7 and 8 the individual males and females illustrated and numbered have had permanent pacemakers implanted for PFHB. Their ancestral links are clearly traced to 3 men (numbers 3, 4 and 5), the sons of the original immigrant to South Africa in generation 1. These 3 men were part of a sibship of 11 and both the former study[1] (D and F) and the present findings show that these 3 brothers were the originators of PFHB in South Africa.

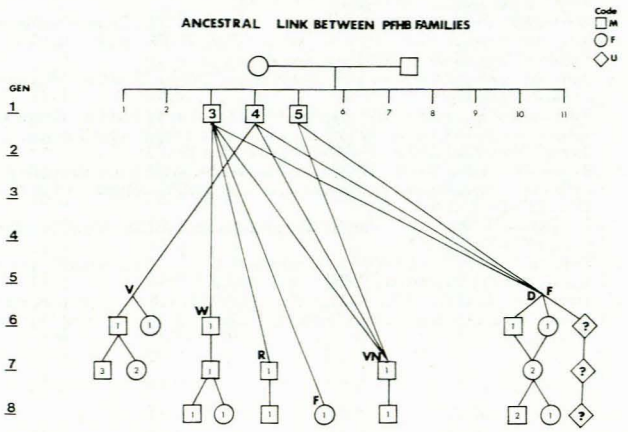

Fig. 1. Schematic diagram of ancestral link between the PFHB families (M = male; F = female; U = unknown; Gen = generation).

Families K, S, Z, VR-F

In contrast with the above 5 families, these 4 families had had no known history of PFHB leading to the implantation of permanent pacemakers, and therefore no one up to now had had a pacemaker implanted. Nevertheless, all 5 families described a familial history of sudden deaths at a comparatively young age (Fig. 2). In generation 5, for instance, the descendants of family K had met or heard of 3 men and 6 women who had died suddenly at a young age. This suggestive history of PFHB led to the tracing of their pedigrees.

Families K, S and Z were found to be linked to the 3 brothers (3, 4 and 5) previously mentioned in generation 1 (Fig. 2). In family K the suggestive history of PFHB was found to be additional to a confirmed history of familial hypercholesterolaemia (FH) (generations 7 - 8 of brother No. 3).

In family S the suggestive history of PFHB was additional to a confirmed history of porphyria (generation 6 of brother No. 3), an observation which had already been substantiated in family VN previously mentioned.

In family Z there was only a suggestive history of PFHB (generations 6 - 7 of brother No. 5).

The last family VR-F exhibited both a suggestive history of PFHB and a confirmed one of porphyria but they were descendants of yet another brother (No. 7 in generation 1). This last observation strengthens the pattern of inheritance of a dominant gene where

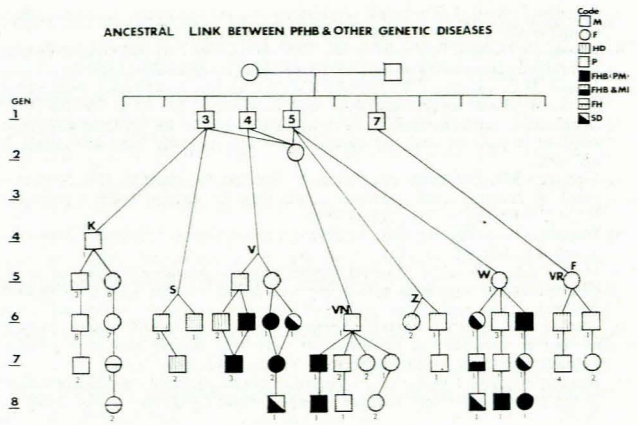

Fig. 2. Schematic diagram of ancestral link between PFHB and other genetic diseases (M = male; F = female; HD = heart disease; P = porphyria; FHB(PM) = progressive familial heart block with pacemaker; FHB & MI = progressive familial heart block and myocardial infarction; FH = familial hypercholesterolaemia; SD = sudden death).

one would expect an approximate 50% occurrence of a disease appearing in the present generation.

The number of individuals traced in all 9 families as well as those of the former study are given in Table I. It must be borne in mind that the line of disease was traced back through a single ancestral parent. The extent of the disease is therefore likely to be much wider than that found in the branches of the families which have so far been identified.

PFHB, FH and porphyria variegata have all been described in the literature as presenting as an autosomal dominant disease.[1,3,4] The unexplained number of sudden deaths, as yet of unknown cause, could therefore be due to the manifestation of PFHB and/or FH in previous generations (Table II).

In the families being studied at present, intermarriage occurred in practically every generation (Table III). Thus, in the case of VN where 7 intermarriages were identified, no cognizance is taken of other intermarriages occurring in the sibship. At generation 2, 1 intermarriage only was of interest to the link with the proband but 8 other intermarriages were identified, 1 each in V, S and K, and a further 5 which have not been followed up. This pattern could be observed at every generation in all pedigrees.

Discussion

The initial immigrant married in South Africa in 1735 and 9 of his 11 children married between 1760 and 1775. Four of these children were sons and are the ancestors of the present families discussed. The remaining 5 daughters have not been traced because the Genealogical Society follows only the male lines. The assumption that some of the daughters may have

TABLE I. TOTALS OF INDIVIDUALS TRACED IN DIFFERENT FAMILIES

Generation	Type I (former study)	Family surnames V	W	R	F	VN	Z	S	K	VR-F
1	2									
2	14									
3	54									
4	+113								10	
5	+ 77								49	
6		6	7				8	10	26	1
7		31	17	3	3	9	2	23	19	24
8		29	25	8	8	21	3	3	19	15
Total	+260	66	49	11	11	30	13	36	123	40

TABLE II. NO. OF SUDDEN DEATHS IN DIFFERENT FAMILIES

Generation	Family surnames V	W	R	F	VN	Z	S	K	VR-F
1				Unknown					
2				Unknown					
3				Unknown					
4								1	
5	2	1			1	3		9	1
6	3	5		3	2	1	6	13	4
7		2					4	1	
8	1	1							
Total	6	9	0	3	3	4	10	24	5

TABLE III. NO. OF INTERMARRIAGES OCCURRING IN EACH GENERATION

Generation	Family surnames V	W	R	F	VN	Z	S	K	VR-F	Total	Other known lines of descendants not traced
1											
2	1				1		1	1		4	5
3					1					1	?
4					3	1			1	5	6
5					1			2		3	16
6					1		1	1		3	6
7										0	1
8										0	0
Total	1				7	1	2	4	1	16	34

had the gene and passed it on to their descendants cannot be excluded. However, to date, none of the pedigrees that could be traced back was linked to any of the daughters. The 4 sons produced 21 children between 1763 and 1790.[2] There is no further data in De Villiers and Pama[2] relating to these children's descendants at generation 3 on Figs 1 and 2. Such links as were found between generation 3 and the present generations (7 and 8) were traced through archival research.

As already mentioned, a dominant disease will affect approximately half a sibship. An estimate of the number of affected individuals arising from the initial immigrant can be made on the basis of the following assumptions: if there were 8 generations of 25 years each (from the 4 sons at generation 1), and on average only 5,25 children were born to each married couple per generation (the 21 children who survived the 4 sons of the initial immigrant give an average of 5,25 children per family), then, since it is expected that half of each sibship will be affected, an estimate of the number of affected individuals in the 8th generation is 2 254 per son. This number multiplied by 4 sons gives a minimum estimate of 9 000 people who have some form of familial heart disease. Two of the assumptions are probably underrated, namely the generation gap of 25 years and a family of 5 children. Young people in the 17th, 18th and 19th centuries tended to be married by their 20th birthday and children (under normal conditions) were born on an average of every 15 months.

This basic estimate has not taken into account descendants of any other children of the initial immigrant, since it has not included the possibility of the appearance of homozygotes. It is known that intermarriages in isolates may lead to the birth of a homozygote. Former studies on FH have shown the reason for the development of this manifestation in certain families in South Africa.[5]

These 9 pedigrees from the 40 referred for investigation thus represent only a small fraction of the problem in the RSA and a conservative estimate of the prevalence of PFHB or familial heart disease is therefore 1 in 500 South Africans of European descent.

Conclusion

PFHB is a disease of considerable magnitude; it is also progressive, as will be shown in Part II. Therefore it is of vital importance that affected people in a much greater section of the population should be identified, followed up and if necessary treated prophylactically by implantation of permanent pacemakers to prevent more unnecessary sudden deaths.

REFERENCES

1. Brink AJ, Torrington M. Progressive familial heart block — two types. *S Afr Med J* 1977; **52:** 53-59.
2. De Villiers CG, Pama C. *Genealogies of Old South African Families.* Cape Town: AA Balkema, 1966.
3. Fredrickson DF, Goldstein JL, Brown MS. Familial hyperlipoproteinemias. In: Stanbury JE, Weingaarden JB, Donald F, Fredrickson DF, eds. *Metabolic Basis of Inherited Disease.* 4th ed. Philadelphia: McGraw-Hill, 1978: 604-655.
4. Dean G. *The Porphyrias. A Story of Inheritance and Environment.* 1st ed. London: Pitman, 1963: 4.
5. Torrington M, Botha JL, Pilcher GJ, Baker SG. Association between familial hypercholesterolaemia and church affiliation. *S Afr Med J* 1984; **65:** 762-767.