PRELIMINARY COMMUNICATIONS

Maternal HL-A Antibodies and Fetal Sex

KARL JOHANSEN, HILLIARD FESTENSTEIN

British Medical Journal, 1974, 4, 202-203

Summary

In a study of 960 pregnancies a significantly higher male to female birth ratio was found among primigravidae who developed HL-A antibodies, which was highest where these were monospecific. In the whole group male births predominated in women with antibodies to HL-A 1 and 11 (first locus) and HL-A 5, 12, and 13 and TYT (second locus).

The influence of maternal parity on the development of HL-A antibodies in pregnancy is well known and has been discussed elsewhere, as have the relative roles of the mature and immature fetus (Burke and Johansen, 1974). Subsequently it was observed that the male fetus appeared to be more strongly antigenic than the female (Johansen *et al.*, 1974), and the results of that study of 960 women are summarized in table I.

TABLE I—Male to Female Birth Ratios Compared with HL-A Antibody Formation and Maternal Parity

Past Obstetric History	Cytotoxic Antibodies during Pregnancy		Total
	Absent	Present	
No previous birth	0.99 a	1.82 a ¹	1.07 x
One previous birth	1.24 b	1.26 b ¹	1.24 y
Two or more previous births	1.54 c	1.10 c ¹	1.40 z

Statistical analysis

- (i) Values for χ^2 with Yates's correction— $a:a^1$, $\chi^2 = 4.02$, $P < 0.05$; $c:c^1$, $\chi^2 = 0.96$, N.S.
 (ii) Analysis for trend (Armitage, 1955)— $a \rightarrow b \rightarrow c$, $\chi^2 = 5.82$, $P < 0.02$; $a^1 \rightarrow b^1 \rightarrow c^1$, $\chi^2 = 1.88$, $P 0.18$; $x \rightarrow y \rightarrow z$, $\chi^2 = 2.75$, $P 0.09$.

The male to female birth ratio in primiparae was 1.82 among 61 patients who developed HL-A antibodies, which was significantly higher than that (0.99) among 384 who did not ($P 0.05$). In their second pregnancy 18.6% of 280 women were found to have antibodies, and the corresponding ratios were 1.26 and 1.24. Among 235 multigravidae the ratios were 1.10 for those (26.8%) with antibodies but 1.54 for those without ($0.4 > P > 0.3$). The overall ratio was higher than expected and though this remained unexplained it could have been attributable to chance. These findings, which were supported by the birth ratios found in the first pregnancy of the secundigravidae concerned, were presented as evidence of interaction between HL-A and unidentified sex-specific histocompatibility systems.

Welsh National School of Medicine, Cardiff CF4 4XN

KARL JOHANSEN, M.B., M.R.C.O.G., Senior Lecturer in Obstetrics and Gynaecology

London Hospital Medical College, London E.1

HILLIARD FESTENSTEIN, M.B., M.R.C.PATH., Reader in Tissue Immunology

Present Investigation

Studies of sex ratios at birth are beset by difficulties which are principally attributable to sampling errors. The subject was extensively reviewed by Stevenson and Bobrow (1967), and though we cannot offer a detailed evaluation of the large variety of individual factors which may influence fetal sex we believe from a parallel study that there is no significant relationship between the development of HL-A antibodies and either maternal age or blood group (Johansen, 1974).

It therefore seemed worthwhile to see whether the predominance of male infants could be related to the development by the mother of antibodies to individual HL-A factors or to groups of antigens. Lymphocyte antibodies had been found in 215 of the total survey of 1,242 pregnant women. The cytotoxic reaction was polyspecific in 22% and weak in 30% of instances, so that in these groups the HL-A identity was not clearly defined. In 48%, however, moderate or strong cytotoxicity was found and in 84% of these one or more HL-A specificities were established.

The male to female ratio was highest (1.5) in this last group and higher (3.3) among primiparae than multiparae (1.2). In 52 women a monospecific antibody was identified, and the corresponding ratios were 2.1 (all parities), 5.0 (primiparae), and 1.7 (multiparae). There was no significant difference in birth ratios for women with antibodies to first (LA) as opposed to second (FOUR) locus antigens.

In the 85 women in whom antibodies were identified 123 HL-A specificities were defined (table II). Irrespective of parity the sex ratios were observed to approach unity for women with antibodies to most HL-A antigens. By contrast an excess of boys (31:8) was found among the women who had formed antibodies to HL-A 1 and 11 (first series) and HL-A 5, 12, and 13 and TYT (second series). There was no corresponding excess of female births in any antibody group, and when the sex ratio among women with antibodies in the male-dominated group (3.9) was compared with the remainder (40:43; ratio 0.93) the difference was found to be highly significant ($P < 0.005$).

TABLE II—Infant Sex Ratios at Birth for Women with Particular HL-A Antibodies

First Series		Second Series	
Antibodies Formed	M.:F. Ratio	Antibodies Formed	M.:F. Ratio
HL-A 1	4:1†	HL-A 5	6:1†
HL-A 2	5:5	HL-A 7	12:10
HL-A 3	2:2	HL-A 8	1:1
HL-A 9	1:2	HL-A 12	7:3†
HL-A 11	4:1†	HL-A 13	6:2†
W 28	1:1	W 05	3:2
W 30	1:1	W 10	5:7
Mo*	1:0	W 14, 15, 17, 21, 22	5:9
		W 27	4:3
		TYT	4:0†
Total	19:13	Total	53:38

†Male-dominated groups.

The comparison between these two groups is drawn on an empirical basis, but HL-A 1 and 11 are recognized for their cross-reactivity, while HL-A 5, 12, and 13 belong to the group originally designated by van Rood *et al.* (1970) as "4a." To attempt to derive conclusions from such small numbers as ours invites criticism but it would be interesting to know whether similar occurrences have been recognized elsewhere.

This work was financed in part by a grant from the London Hospital Research Fund.

References

- Armitage, P. (1955). *Biometrics*, 11, 375.
 Burke, J., and Johansen, K. (1974). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 81, 222.

- Johansen, K. (1974). Thesis submitted to University of London.
 Johansen, K., Festenstein, H., and Burke, J. (1974). *Journal of Obstetrics and Gynaecology of the British Commonwealth*. In press.
 Stevenson, A. C., and Bobrow, M. (1967). *Journal of Medical Genetics*, 4, 190.
 van Rood, J. J., van Leeuwen, A., and Zweerus, R. (1970). *Histocompatibility Testing*, p. 92. Copenhagen, Munksgaard.

MEDICAL MEMORANDA

Effects of Calcitonin Therapy in Deafness Associated with Paget's Disease of Bone

W. H. MOFFATT, JOHN D. MORROW,
 NOREEN SIMPSON

British Medical Journal, 1974, 4, 203

Deafness has long been recognized as a complication of Paget's disease of bone. Shai *et al.* (1971) showed that like other manifestations of the disease this may respond to calcitonin therapy and is not necessarily irreversible. We describe a case of deafness associated with Paget's disease substantially improved by calcitonin and believe this to be the first such report from the United Kingdom.

Case Report

A 73-year-old man attended the Greenisland Hospital outpatient clinic in September 1972 complaining of insidious deterioration of gait and increasing deafness after a crippling attack of sciatica in February. For the past three months he had suffered backache and paraesthesiae in the legs. A routine x-ray film in 1968 when he was symptom free had shown extensive Paget's disease of the spine.

Examination showed a small, cheerful man, badly bent and walking hesitantly with a stick. His severe deafness made history taking laborious. His blood pressure was 190/100 mm Hg and there was hypertensive scarring of both fundi. The right clavicle was prominent and enlarged. Despite his complaints his legs were normally strong and there was no evidence of pyramidal damage. Touch and pinprick sensations were impaired in the left foot and vibration sense was reduced in the left ankle. He was admitted to hospital for investigation one week later.

Haemoglobin was 16.8 g/100 ml, blood urea was 30 mg/100 ml, serum calcium and phosphate were within normal limits, and serum alkaline phosphatase was 60 King-Armstrong units. Radiographically the skull was normal but there was extensive Paget's disease of the right shoulder, lumbar spine, pelvis, and femora. He was examined at the Royal Victoria Hospital by one of us (N.S.) and issued with a hearing aid.

Calcitonin therapy was begun on 4 November, the initial dose of 40 M.R.C. units of porcine calcitonin intramuscularly twice a day being increased to 80 M.R.C. units twice daily on 23 November. Within a week of starting treatment there was subjective improvement and the patient walked without a stick or support. There was a gradual improvement in posture. The weekly serum alkaline phosphatase estimation fluctuated between 60 and 80 King-Armstrong units. When the calcitonin dosage could be reduced to 80 M.R.C. units daily he was discharged home fully independent (18 December).

Greenisland Hospital, Newtownabbey, Northern Ireland

W. H. MOFFATT, M.B., F.R.C.P.I., Consultant Physician in Geriatric Medicine
 JOHN D. MORROW, M.B., B.Ch., Medical Assistant in Geriatric Medicine

Royal Victoria Hospital, Belfast

NOREEN SIMPSON, M.B., D.L.O., Medical Assistant, Audiometry Department

He regularly attended the follow-up clinic and remained symptom free. When seen on 21 March 1973 he had discarded his hearing aid and could hear a low-pitched voice at 10 ft (3 m). This satisfactory state persisted and the serum alkaline phosphatase fell to 33 King-Armstrong units. Despite his lack of symptoms the sensory deficit in the left foot remained and may have been age-related.

Comparison was made between the original pure-tone audiometry findings at the hearing-aid clinic in November 1972 and recordings in April 1973. The results are shown in the table and are substantially in accord with those of Shai *et al.* (1971), in that improvement was significant (15 db or more) in the lower frequencies while the higher frequency deficiencies were unaffected. Low-frequency improvement was more marked on the left but speech discrimination was significantly better in the right ear.

Pure-tone Audiogram Data; Air Conduction Component. Values Represent decibels required for Detection. Change of 15 db is significant

	Date	Frequency (Hz)					
		250	500	1,000	2,000	4,000	8,000
Right ear	8/11/72	60	55	50	50	80	70
	18/4/73	40	50	45	45	75	
Left ear	8/11/72	55	45	45	60	80	
	18/4/73	25	30	25	50	75	

Comment

Mayer (1913) first showed an association between deafness and Paget's disease, thus providing the stimulus for further study of the temporal bone in the disease (Anson and Wilson, 1937; Tamari, 1942) and for attempts to correlate the site and extent of bone distortion with audiometric findings (Clemis *et al.*, 1967; Henkin *et al.*, 1972). This correlation was inexact but the work of Clemis *et al.* (1967), in particular, established that the hearing loss was greater than could be accounted for by ageing alone and that, in agreement with our findings, it had no hereditary basis or relationship to past or present aural infection.

Whatever the causation Paget's deafness was incurable until the discovery of calcitonin, and we can find no record of improvement with any other agent.

Since most pathological and x-ray studies have been carried out in subjects with gross temporal bone destruction we recognize how valuable temporal bone tomography would have been in our patient, whose skull x-ray picture was apparently normal. We also agree with the suggestion that impedance audiometry should be a standard investigation in Paget's deafness, thereby defining more accurately the role of the stapes in this condition (O'Neill, 1973).

Our thanks are due to Armour Pharmaceutical Company Limited for initial supplies of Calcitare and for much help and advice. We are grateful to Miss J. Printer for typing the manuscript.

References

- Anson, J. B., and Wilson, J. G. (1937). *Archives of Otolaryngology*, 25, 560.
 Clemis, J. D., *et al.* (1967). *Annals of Otolaryngology and Rhinology*, 76, 611.
 Henkin, R. I., Lifschitz, M. D., and Larson, A. L. (1972). *American Journal of the Medical Sciences*, 263, 383.
 Mayer, O. (1913). *Internationales Zentralblatt für Ohrenheilkunde*, 11, 530.
 O'Neill, P. B. (1973). *British Medical Journal*, 1, 744.
 Shai, F., Baker, R. K., and Wallach, S. (1971). *Journal of Clinical Investigation*, 50, 1927.
 Tamari, M. (1942). *Annals of Otolaryngology and Rhinology*, 51, 170.