Was Young's syndrome caused by exposure to mercury in childhood?

W F Hendry, R P A'Hern, P J Cole

Abstract

***Objective*—To determine whether the incidence of chronic sinusitis, bronchitis, or bronchiectasis in men with obstructive azoospermia (Young's syndrome) has fallen in men born after 1955 when calomel (mercurous chloride) was removed from teething powders and worm medication in the United Kingdom.**

***Design*—A prospective study of aetiological factors in subfertile men with epididymal obstruction operated on between 1975 and 1993.**

***Setting*—Central London.**

***Subjects*—274 men with obstructive azoospermia undergoing epididymovasostomy; date of birth was recorded and illness in childhood, persistent nasal or respiratory symptoms, and previous urinary or genital infection were asked about.**

***Main outcome measure*—Site of epididymal block and association with possible aetiological factors, related to date of birth.**

***Results*—146 men had hold up in the head of the epididymis (capital blocks): 119 (82%) had Young's syndrome, and 11 gave a definite history of pink disease (mercury intoxication) in childhood. 128 had obstruction lower down towards the tail of the epididymis (caudal blocks): 64 (50%) had a history of genital or urinary infection, and only three had Young's syndrome; none had had pink disease. The incidence of Young's syndrome fell significantly from 114 (50%) of 227 men born up to 1955 to eight (17%) of 47 men born since then.**

***Conclusions*—The decline in incidence of Young's syndrome in those born after 1955 is similar to that observed with pink disease, suggesting that both conditions may have had a similar aetiology—mercury intoxication.**

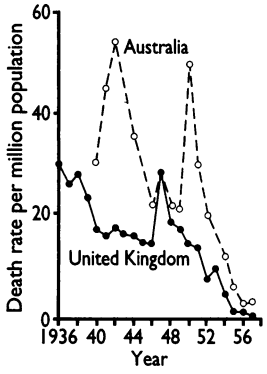

FIG 1—*Death rate for pink disease (reproduced with permission of the Medical Journal of Australia[15])*

Introduction

The presence of chronic sinusitis and bronchitis or bronchiectasis in over half of men with obstructive azoospermia was first described from the north of England by Young in 1970, and further cases were documented shortly thereafter in France.[1,2] Since then, large series of patients with Young's syndrome have been documented in reports from the United Kingdom, Australia, and France, but only sporadic cases have been reported in the United States.[3-8] The testicular obstruction in these cases lies in the efferent ductules in the head of the epididymis,[2] whereas in cases occurring after an infection the block is lower down towards the tail.[9] The efferent ductules are lined by ciliated columnar epithelium similar to that lining the nasal and respiratory passages, whereas the duct of the epididymis is lined by stratified columnar epithelium with microvilli.[10] The association between obstructive azoospermia and chronic nasal and respiratory disease is therefore likely to be due to a common defect in the function of the ciliated columnar epithelium, which is found in both sites.

Earlier studies have shown significantly impaired mucociliary clearance in patients with Young's syndrome[11] even though ciliary beat frequency was normal[12] and electron microscopy showed no ultrastructural defects in the cilia.[3] The viscous, creamy yellow fluid seen at operation within the distended tubules in the head of the epididymis in patients with Young's syndrome is recognisably different from the runny, milky white fluid found in caudal epididymal blocks occurring after infection. Histochemical studies using frozen sections showed that this difference was due to abnormal accumulation of lipid within the epithelium and lumen of the efferent ductules in men with Young's syndrome; this was not seen in the other groups.[9]

The history given by patients with Young's syndrome was nearly always the same: a febrile illness in early childhood, usually associated with a respiratory infection, followed by development of chronic sinusitis with nasal polyps, persistent productive cough, recurrent bronchitis, and in some cases bronchiectasis. The medical features of the respiratory aspects of Young's syndrome have been documented by Handelsman *et al.*[5]

In some men with Young's syndrome, a definite history of pink disease in childhood was forthcoming, suggesting a possible aetiological connection. Pink disease was caused by mercury intoxication,[13] the mercury being released from normally insoluble calomel (mercurous chloride) in teething powders or worm medication under certain intestinal conditions.[14] After considerable controversy, products containing calomel were withdrawn from sale in the United Kingdom and Australia in 1955. Pink disease then disappeared (fig 1), apart from a few isolated cases.[15-17] If Young's syndrome and pink disease shared a common aetiology, the syndrome would also be expected to disappear in men born after 1955. To test this hypothesis we related the dates of birth of a large number of subfertile men with obstructive azoospermia to the site of epididymal obstruction, coexisting nasal or respiratory disease, and any past history of pink disease.

Patients and methods

Between 1975 and 1993, 274 azoospermic men presenting to a single consultant urologist underwent epididymovasostomies for epididymal obstruction. The year of birth was recorded, and they were asked about any history of illness in early childhood of chronic or persistent sinusitis, bronchitis, or bronchiectasis and previous genital or urinary infection. After full investigation including physical examination, seminal analysis, and measurement of hormone concentrations and antisperm antibodies, they underwent scrotal exploration under general anaesthesia.[18] The site of obstruction in the epididymis was established by visual inspection with magnification, supplemented by a photographic record early in the

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series. Patency of the vasa deferentia was tested by vasography, and a testicular biopsy specimen was taken. Patients were classified into those with distension, usually symmetrical, strictly confined to the head of the epididymis (capital blocks), and those with distended tubules extending further down the epididymis on one or both sides towards the tail (caudal blocks). These changes have been described in more detail and illustrated elsewhere.[9 18] Epididymovasostomy was done, and the men were followed whenever possible by seminal analysis repeated at intervals of three months, and inquiry was made about pregnancy in female partners. All men with capital blocks operated on since 1982 received carbocisteine 275 mg thrice daily for 6-12 months.

Results

Of the 274 men, 122 (45%) had Young's syndrome. This association was seen in 114 (50%) of 227 men born before 1956, but in only eight (17%) of 47 men born since then ($\chi^2 = 16{\cdot}1$, $p < 0{\cdot}001$). A total of 119 men with Young's syndrome had capital blocks and only three had caudal epididymal blocks ($\chi^2 = 170$, $p < 0{\cdot}001$). This confirms the close association between chronic nasorespiratory disease and hold up in the efferent ductules in the head of the epididymis.

Among the 146 men with capital blocks, 12 claimed to have fathered children in the past, and progressive deterioration in the sperm count culminating in azoospermia was observed in four. Thirty three (23%) had bronchiectasis, 44 (30%) had chronic bronchitis, and 42 (29%) had persistent sinusitis, leaving 27 (18%) with no such complaints. Eleven (8%) gave a definite history of pink disease in infancy (table I). Only 12 (8%) of the men with capital blocks had had genital or urinary infection.

TABLE I—*Characteristics of men with a definite history of pink disease in childhood*

Case No	Year of birth	Sperm count (M/ml)	Chest problems	Findings at operation
1	1946	0	Bronchiectasis	Right capital block, left fibrosis
2	1951	0	Bronchiectasis	Bilateral capital blocks
3	1953	0	Bronchiectasis	Bilateral capital blocks
4	1947	0	Bronchitis	Bilateral capital blocks
5	1949	0	Bronchitis	Left capital block, right atrophic
6	1952	0	Bronchitis	Bilateral capital blocks
7	1953	0	Sinusitis	Bilateral capital blocks
8	1946	0	None	Left capital block, right atrophic
9	1948	0	None	Bilateral capital blocks
10	1950	0	None	Bilateral capital blocks
11	1952	0	None	Bilateral capital blocks

TABLE II—*Year of birth of men with Young's syndrome, capital and caudal epididymal block*

Year of birth	No with caudal blocks	No with capital blocks	No with Young's syndrome	Death rate from pink disease[16]
1938 or before	7	9	6	
1939	2	1	1	
1940	4	0	0	
1941	1	2	2	
1942	3	4	3	
1943	6	4	3	
1944	5	5	4	
1945	3	7	6	
1946	3	7	6	
1947	5	17	14	
1948	3	10	7	
1949	4	10	7	
1950	6	13	12	34
1951	5	13	11	34
1952	6	17	15	15
1953	7	7	8	19
1954	8	4	3	8
1955	12	7	6	4
1956	4	0	0	3
1957	6	3	2	2
1958	7	2	1	0
1959	3	1	1	1
1960	4	1	0	1
1961	4	0	1	
1962	1	0	0	
1963	4	0	1	
1964 or later	5	2	2	
Total	116	140	116	

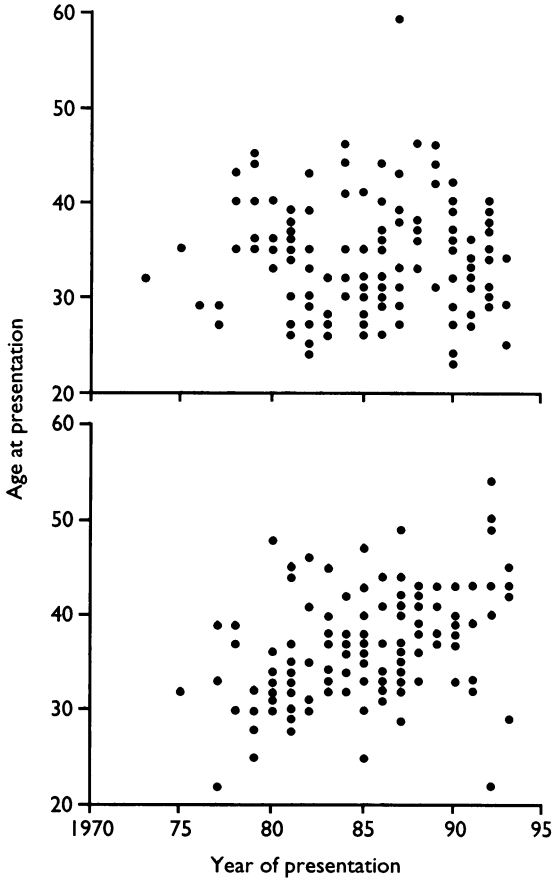

FIG 2—*Age distribution at presentation of patients with caudal epididymal blocks (top; R = −0·02, NS) and patients with capital epididymal blocks (bottom; R = 0·39, p < 0·001)*

Table II shows the years of birth of those with Young's syndrome and those with capital and caudal epididymal blocks where they may be compared with the national death rate for infant boys from pink disease in 1950-62.[16] The fall in the incidence of Young's syndrome and capital blocks in those born after 1955 is obvious, resembling the decline in incidence of pink disease. Four of the nine men with capital blocks born after 1955 grew up abroad (Kenya 1, South Africa 1, Middle East 1, Sicily 1); if these are discounted, it can fairly be said that only isolated cases have been seen in those born in the United Kingdom since 1955. No such decline in incidence has been seen in those with caudal blocks.

Among the 128 men with caudal epididymal blocks, only three gave a history of either bronchiectasis (1), chronic bronchitis (1), or persistent sinusitis (1) ($\chi^2 = 170$ for difference from men with capital blocks, $p < 0{\cdot}001$). None gave a history of pink disease in childhood. Sixty four (50%) gave a history of urinary or genital infection ($\chi^2 = 57{\cdot}3$ for difference, $p < 0{\cdot}001$).

The age distribution of patients at presentation would be expected to be independent of year of presentation if there was no change in aetiological factors. Figure 2 shows this independence in patients with caudal blocks and a positive correlation between age and year of presentation in patients with capital blocks. One of the contributing factors to this is that few patients who were born after 1955 presented with epidymal obstruction (fig 3). Men born before 1940 would have been over 35 years old when this

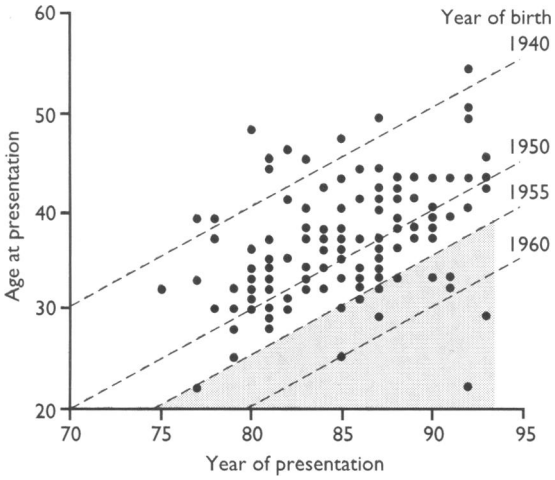

FIG 3—*Patients with capital epididymal blocks related by year of birth to age distribution at presentation. Four of the men born after 1955 grew up abroad*

study started and less likely to present with fertility problems.

Discussion

Warkany, who established the link between mercury and pink disease, commented in a review that there is nothing more dead than a dead disease.[17] The results of this study indicate that the resulting problems may, in fact, live on since there is a relation between pink disease in childhood and Young's syndrome in adult life and, by inference, between both conditions and mercury intoxication.

Although the toxic effects of mercury are well documented,[19 20] this long term effect on reproduction has not been described before.[21 22] Mercury inhibits enzymes containing sulphydryl by reacting with thiols to form mercaptides.[23] Cilia, like spermatozoa, rely on glycolysis for energy, and impairment of sperm motility has been observed with exposure to mercury.[24] Other examples of enzyme inhibition have been well documented in spermatozoa and their effects noted in the epididymis. Chemicals such as α-chlorhydrin and 6-chloro-6-deoxy glucose, which block glyceraldehyde 3-phosphate dehydrogenase, lead to acute cystic change in the efferent ductules and infertility in animals.[25] The stasis that developed in the ductules in our men with Young's syndrome was much more gradual, since some were previously fertile, and seemed to be due to accumulation of lipid in the ductules.[9] It is not known why this should happen, although it may be noted that patchy hold up in the ductules has commonly been seen at necropsy in old men.[26] Premature change in mitochondrial DNA has been put forward as one possible explanation.

The results of epididymovasostomy were much better in the group with postinfective caudal epididymal blocks (patency 52%, pregnancies 38%) than in those with holdup in the head of the epididymis, 82% of whom had Young's syndrome (patency 12%, pregnancies 3%). Significantly better results were obtained in the latter group in those receiving adjuvant carbocisteine (patency 23%, pregnancy 7%) compared with those who had no adjuvant therapy (patency 2·2%, no pregnancies).[9] Improvement in nasal and respiratory symptoms was noted subjectively by the men receiving adjuvant carbocisteine. Even with adjuvant therapy, however, the results were much poorer than those obtained in men with postinfective blocks lower in the epididymis, presumably partly because of poor flow characteristics in Young's syndrome. With the decline in incidence of capital blocks, surgeons can look forward to much better results of reconstruction for obstructive azoospermia.

The geographical differences in incidence of Young's syndrome are important. Sale of calomel was discouraged by the Food and Drug Administration in the United States in 1933,[17] and remarkably few examples of Young's syndrome have been reported there.[6 7] On the other hand, as Warkany commented, wherever the British flag flew, calomel was an ingredient of popular medications, probably because it induced sweating and acted as a purgative.[17] Although there were regional differences in incidence,[27] it has been estimated that as many as a quarter of infants in Sheffield and a third in Warwickshire were receiving teething powders containing mercury.[28 29] The largest series of Young's syndrome have been reported from the United Kingdom and from Australia, where the incidence of pink disease was highest until the sale of calomel was prohibited.[15]

It should not be expected, however, that Young's syndrome will disappear completely. Teething powders containing calomel were still on sale in the United Kingdom as late as 1966, and isolated reports of pink disease have continued to appear, associated with mercury in such varied sources as vermifuges, ointments, dusting powders, gammaglobulin, and fungicides on wheat seed. Mercury intoxication has also been recorded in dentists, and from industrial pollution, house paint, and metallic mercury. Mercury is still on sale in London in 1993 in skin lighteners[30] and is being prescribed in ethnic remedies.[31] Previous studies suggested that there were no long term sequelae of pink disease.[32] This study shows that this is not so and emphasises the vital importance of recognising and eliminating such toxic factors from our environment.

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Multicentre randomised double bind crossover trial on contamination of conventional ties and bow ties in routine obstetric and gynaecological practice

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Abstract

***Objective*—To assess level of contamination of neckwear worn by gynaecologists and obstetricians during routine working week.**

***Design*—Multicentre randomised double blind crossover trial. Participants wore the same conventional ties for three days in one week and bow ties for the same period in second week.**

***Setting*—Two teaching and three district general hospitals in the midlands, Wales, and north England.**

***Subjects*—15 registrars and senior registrars.**

***Interventions*—A swab soaked in sterile saline was taken from specific area on ties at end of first and third working days and sent in transport medium for culture on chocolatised blood and MacConkey agar for 48 hours.**

***Main outcome measures*—Level of bacteriological growth assessed semiquantitatively (0 for no contamination; +++ for heavy contamination) after swabs had been cultured. At end of study the participants completed a questionnaire to assess their attitude toward wearing different types of necktie.**

***Results*—12 doctors (80%) completed the study. Although bow ties were significantly less contaminated at end of first working day ($z = -2{\cdot}354$, $p = 0{\cdot}019$), this difference was not maintained; there was no difference in level of contamination on third day. Level of contamination did not increase between first and third day of wearing the same garment. One of the 10 doctors who returned the questionnaire found the bow tie very uncomfortable. All participants would consider wearing a bow tie if it proved to be less contaminated than a conventional tie.**

***Conclusions*—Although a significant difference in contamination was established between conventional and bow ties on first day of study, this difference was not confirmed on third day and there is unlikely to be any real association between tie type and bacterial contamination. Because of its negative image and difficulty to tie, the bow tie will probably remain a minority fashion.**

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Introduction

Throughout the nineteenth century the "once round" tie with a small flat bow over an upright, stiffened collar was the usual attire of medical practitioners.[1] As fashions have changed the wearing of bow ties has decreased, and bow ties are now worn almost exclusively by a small proportion of obstetricians, who often argue that, in labour wards soiled with blood and amniotic fluid, bow ties are more hygienic than conventional ties. There is at present no evidence to support this argument. Therefore, we assessed the contamination of conventional ties and bow ties worn by obstetricians during a typical working week.

Subjects and methods

Doctors from two teaching and three district general hospitals in the midlands, Wales, and north England were recruited to the study. The participants were given a new conventional tie and bow tie together with illustrated instructions on how to tie them. The participants wore one tie for three days in one week, and the other tie for the same period in the second week: subjects were randomised by means of sealed opaque envelopes to wear either the bow tie or the conventional tie first.

A swab soaked in sterile saline was taken by the participants from the tip of the ties—an area with a radius of 2 cm on the conventional tie (obtuse angle) and 2 cm on the bow tie (acute angle) at the end of the first and third working day and sent in the transport medium for assessment of bacteriological growth. All the swabs were analysed by one of us (DS). The level of contamination was assessed with a semiquantitative system (from 0 for no contamination to +++ for heavy contamination) after the swabs had been cultured on chocolatised blood and MacConkey agar aerobically at 37°C for 48 hours.

At the end of the study the participants completed a questionnaire to assess their attitude towards wearing the different types of necktie: the participants were asked about their usual neckwear, their habit of wearing white coats, whether they felt comfortable wearing a conventional tie or bow tie, which type of neckwear they thought patients and members of staff preferred them to wear, and if they would consider wearing an alternative tie if the study showed it to be less contaminated.

STATISTICAL ANALYSIS

The data were analysed in two ways. Firstly, the degree and type of bacterial growth were ignored, and ties were simply classified according to whether there was evidence of contamination. McNemar's test was used to make comparisons (bow tie *v* conventional tie on first day; bow tie *v* conventional tie on third day; bow tie, first day *v* third day; and conventional tie, first day *v* third day). The comparisons were repeated with a change in the classification so that a score of 0 or + was counted as no contamination while a score of ++ or +++ was counted as contamination. Although this method takes account of the pairing in the study design, it does not make use of the degree of growth identified.

The second method of analysis used was to compare, in pairs, the total number of positives in the four categories (first day and third day for bow tie and conventional tie) with the Wilcoxon signed ranking test for matched pairs. The total for each doctor for each of the four categories was calculated by simply summing the score across all six combinations of media type and bacteria type. A conservative significance