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Age–sex distribution of various diseases with particular reference to toxoplasmic lymphadenopathy

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SUMMARY

An account is given of some human diseases which affect one sex more than the other.

An age–sex relationship has been noted among British patients with acquired toxoplasmic lymphadenopathy. This is compared with the findings of other European workers.

A possible explanation is offered taking all these diseases into consideration together with some of the experimental work done in animals and some of the variations in immunological responses by man.

DISEASES OF MAN WHICH AFFECT ONE SEX MORE THAN THE OTHER

We do not propose to present a comprehensive list of these but simply to draw attention to some of them.

Sub-acute sclerosing panencephalitis affects boys three times more frequently than girls and almost all patients are under 15 years of age at the time of onset. In seven reported series (Connolly, Allen, Hurwitz & Millar, 1967; Pettay *et al.* 1971; Jabbour *et al.* 1972; Baguley & Glasgow, 1973; Dick, 1973; Green & Wirtschafter, 1973; McDonald, Kipps & Learg, 1974) 219 of 289 patients were boys.

Bjorvatin & Wolontis (1974) have reported that in Stockholm mumps meningoencephalitis occurred three times as commonly in boys under 15 years as in girls and that in patients aged 15 years or more the ratio was nearer 3 to 2. Earlier Kane & Enders (1945) showed that mumps encephalitis with salivary gland involvement tended to affect older patients (average age 15 years) whereas mumps encephalitis without salivary gland involvement affected younger ones (average age 6·5 years). Twelve of 17 in the former group were males and 13 of 16 in the latter.

Intussusception occurs mainly in infants and young children under 3 years of age, affects boys twice as frequently as girls and has been shown to be associated with recent adenovirus infection, mainly types 1, 2 and 5 (Potter & Zachary, 1964).

By contrast, thyrotoxicosis, Hashimoto's disease and primary biliary cirrhosis occur almost exclusively in adulthood and affect women much more frequently than men. The ratios of women to men are – thyrotoxicosis, from 10 to 1, to 4 to 1 (Morgans, 1964); Hashimoto's disease, 9 to 1 (Skillern, 1964); and primary biliary cirrhosis, 7 or more to 1 (Rubin, Schaffner & Popper, 1965; Walker, Doniach, Roitt & Sherlock, 1965; Goudie, Macsween & Goldberg, 1966).

Discoid lupus erythematosus occurs mainly in patients aged between 20 and 40 years and only seldom under 15 years; females are affected three times as commonly as males (Epstein & Tuffanelli, 1966). Disseminate lupus affects mainly patients in their late 'teens, twenties and thirties; 78–96 % of them are women (Dubois, 1966).

In a group of 100 patients with myasthenia gravis whose average age was 41 years, there were 76 women and 24 men (Feltkamp *et al.* 1974). In another series of 54 'juveniles' (Bundey, Doniach & Soothill, 1972) with myasthenia gravis who were aged under 20 years at the time of onset, 42 were girls and 12 were boys – roughly the same ratio as in the adults. However, only three patients were of the early onset type.

Rheumatoid arthritis is three times more common in women than men and the onset in the majority of patients is between 25 and 54 years (Copeman, 1964). In some respects Still's disease may be regarded as the juvenile equivalent of rheumatoid arthritis; in this disease the ratio of the sexes is nearer unity (Bywaters, 1967). Recently Goel & Shanks (1974) have classified Still's disease into 'early onset' and 'late onset' types. They found that the male to female ratio in the former was 3:2 and in the latter 2:3.

Two-thirds of patients with acquired haemolytic anaemias are females (Sacks, Workman & Jahn, 1952). In an analysis of the several groups of auto-immune haemolytic anaemia Dacie (1962) showed that, of the cold antibody type, all but one of those patients with paroxysmal haemoglobinura were under 20 years of age and more males were affected than females, all of the idiopathic type were over 30 years and the male to female ratio was 1:3, and all of the secondary type were over 20 years and the male to female ratio was 1:2. Of those with warm antibody, 87 % of the secondary type were over 25 years and females predominated by 2:1, whereas in the idiopathic type there were more young patients (only 73 % over 25 years) and the females again predominated but by only 5:4.

While Hodgkin's disease occurs more frequently in males, the nodular sclerosing type occurs more often in females. Four surveys (Hanson, 1964; Keller, Kaplan, Lukes & Rappaport, 1968; Henry, 1971; Prosnitz, Nuland & Kligerman, 1972) comprising 633 patients (373 males and 260 females) report nodular sclerosis in 82 of the males (22 %) and in 107 of the females (41 %). Hodgkin's disease is relatively rare in children. Two reports (Kelly, 1965; Hays, Hittle, Isaacs & Karon, 1972) when combined together show that of 22 children under 10 years, only 4 (19 %) were girls while of 40 children age 10–15 years, 18 (45 %) were girls. Miller (1966)

reported that the death rate from this disease before the age of 10 years was six times higher in boys and that after this age the ratio of male to female deaths was 1·5 to 1·0.

Other conditions in which males are affected more frequently are cot deaths and congenital hypertrophic pyloric stenosis. Clinical manifestations of adenovirus type 7 infection are twice as frequent in males at all ages (*British Medical Journal*, 1973*a*) as are those with acute heptatitis B infections (*British Medical Journal*, 1973*b*). Rhinoviruses (both M and H) have been isolated approximately twice as frequently from male patients aged under 15 years than from females; the ratio was reversed in those aged 15 years or over (P.H.L.S., 1974, unpublished data). The inference is that swabs were taken from these patients because they were more ill than is usual with a common cold.

TOXOPLASMIC LYMPHADENOPATHY IN BRITAIN

Materials and methods

Dye tests (Sabin & Feldman, 1948) were done on sera submitted to our laboratories for toxoplasma antibody studies. Paired sera were tested in some instances but only rarely was it possible to show a rising titre. This was because the first specimen was often taken late in the disease when the titre was already maximal or possibly even past the peak. In some instances a lymph node was examined histologically when the changes described by Piringer-Kuchinka (1952) were found in those patients who had high antibody titres. More rarely, unfixed tissue was available for mouse inoculation; *Toxoplasma gondii* was then isolated in most of the instances when the antibody titres were high.

Results

Only those patients who were found to have high titre toxoplasma antibodies and for whom we were given a history of enlarged lymph nodes are included in this report. In all, there were 1127 such patients. Over 1000 of these were examined in the years 1967–72. Table 1 shows that the numbers rose gradually throughout this period. This rise is more likely to be due to increasing awareness among clinicians of toxoplasmic lymphadenopathy as a clinical entity than to an increasing incidence.

No information as to age or sex was provided for 143 patients. Of the remaining 984, 498 were males and 486 were females. This equality of distribution between the sexes was found in each of the four centres – Leeds, Sheffield, Swansea and Tooting. A third of the patients was aged 15–24 years, a quarter 25–34 years and a fifth 5–14 years. Table 2 shows that the age distribution was similar in each of the four centres but there were more of the younger age groups in the Sheffield area. This may reflect the high local level of general paediatric interest.

When each age group was examined for sex distribution it was found that in all areas more males were affected in each of the two under-15 age groups, more females in the four 25 years and over age groups and that the sexes were equally

Table 1. *Numbers of patients with toxoplasmic lymphadenopathy in Britain in the years* 1967–1972

Year	Number
1967	91
1968	146
1969	163
1970	185
1971	222
1972	216

Table 2. *Percentages of patients with toxoplasmic lymphadenopathy in each age group for each of the four British centres*

Age group	Leeds	Sheffield	Swansea	Tooting
0–4	5	9	7	3
5–14	21	34	14	14
15–24	36	29	37	36
25–34	23	14	25	26
35–44	8	6	11	11
45–54	4	7	3	6
55 or more	3	1	3	4

Table 3. *Sex distribution of toxoplasmic lymphadenopathy for different age groups in Britain*

	Numbers affected			
Age group	Both sexes	Males	Females	Ratio of males:females
0–4	50	41	9	1·0:0·22
5–14	184	128	56	1·0:0·44
15–24	349	175	174	1·0:1·0
25–34	233	94	139	1·0:1·48
35–44	89	36	53	1·0:1·47
45–54	49	13	36	1·0:2·77
55 or more	30	11	19	1·0:1·73

affected in the 15 to 24-years age group. The combined figures for all the centres are shown in Table 3.

TOXOPLASMIC LYMPHADENOPATHY IN OTHER EUROPEAN COUNTRIES

The results of 17 European reports are summarized in Tables 4 and 5. The former presents 12 of them in which there was sufficient published information to allow of age–sex classification somewhat comparable with our groupings in Table 3. Table 5 is a summary of the other five reports in which there was less information on the age and sex of the patients.

On the whole, in childhood, boys were affected three times as commonly as girls. During adolescence the sexes were affected equally while in adulthood women were affected three times as frequently as men (Table 4). In the five series summarized in Table 5, most of the patients were adult and most were female.

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Table 4. *Age–sex distribution of toxoplasmic lymphadenopathy in European countries*

		Childhood			Adolescence			Adulthood				
Country	Author	Age range	M	F	Age range	M	F	Age range	M	F	Total	Biopsy
Austria	Piringer-Kuchinka *et al.* (1958)	<11	1	0	11–20	8	5	>21	6	42	62	All histological confirmation
Czechoslovakia												
1	Kouba, Jira & Hubner (1974)	<15	4	1	15–19	7	5	>20	8	31	56	No reference to biopsy
2	Mathernova & Catar (pers. com.)	<15	2	0	15–24	9	15	>25	6	17	49	No reference to biopsy
Denmark												
1	Siim (1951, 1955, 1956)	<15	7	3	15–24	3	4	>25	1	2	20	Biopsy on most adults and some of children
2	Bang (1957)	<15	0	0	15–24	2	0	>25	1	6	9	All histological confirmation
France												
1	Lelong *et al.* (1960)	<15	118	41	15–24	8	18	>25	9	10	204	Confirmed by isolation in 18
2	Lemaire, Debray, Blanchon & You Kim Yean (1965)	<15	2	0	15–24	5	4	>25	0	3	14	Biopsy on 6. One isolation and 5 histological examinations
Germany	Roth & Piekarski (1959)	<15	0	0	15–24	3	4	>25	1	5	13	All histological confirmation
Italy	Campesi & La Franca (1965)	<15	1	0	15–24	2	0	>15	1	2	6	One biopsy
Switzerland	Bamler & Schulthess (1955)	<15	1	0	15–24	6	1	>25	4	4	16	All histological confirmation
Total			136	45		53	56		37	122	449	

Table 5. *Toxoplasmic lymphadenopathy in more European centres*

Country	Author	Number of patients in different age groups	Male	Female	Total	Biopsy
France	Piguet, Christol, Bilski-Pasquier & Bouser (1966)	9 of 15–19 years 19 of 20–35 years 2 over 35 years	10	20	30	Biopsy on 3
Germany 1	Lennert (1961, 1969)	5 in first decade, 45 second, 88 third, 49 fourth and later	76	111	187	Biopsy for histology on all
Germany 2	Mohr & Fliedner (1969)	Mostly 15–28 years	Females greatly predominated		206	Histology on 95
Sweden	Huldt (1960)	3 under 15 years 2 of 16–20 years 23 of over 20 years	6	22	28	Biopsy on 12

With the exception of the three series by Siim (1951, 1955, 1956) and that by Lelong, Bernard, Desmonts & Couvreur (1960), infections in adolescents and adults appear to have been described more frequently than in children. This may in part have been due to a reluctance to perform biopsy on children. So, young patients would tend to be excluded from those series in which the diagnosis was based on both serological and histological evidence. These series can be identified by the information in the biopsy columns of Tables 4 and 5. There is also an understandable reluctance to perform venepuncture on younger children unless it is thought to be really necessary.

The series reported by Piringer-Kuchinka, Martin & Thalhammer from Vienna (1958) amplifies an earlier report (Piringer-Kuchinka, 1952). Both this and the series reported by Bang from Copenhagen (1957) show a preponderance of females among the affected adults which is similar to that in Tenhunen's series from Finland (1964). This last is not summarized in the tables. It includes those patients reported in earlier series by Saxén & Saxén (1959) and by Saxén, Saxén & Tenhunen (1962). All 118 patients submitted to biopsy. Only 23 were aged 20 years or less and the youngest of these was 11 years; 20 of these 23 were females. Of the remaining 95 aged over 20 years, 88 were women. So, in all age groups from adolescence onwards, females are seen to be affected far more frequently than males in Finland.

DISCUSSION ON TOXOPLASMIC LYMPHADENOPATHY

Several factors must be taken into consideration when attempting to find explanations of this unusual age–sex distribution. Firstly, the infection rates in the sexes might be expected to be different at different ages. On the whole boys attract dirt more easily than girls and so may be more liable to contract infection from soil and dust containing sporulated oocysts derived from cat faeces. Women may be more prone to infection than men, partly because it is they who are left with the care of the household pets rather than their husbands and partly because they are more exposed, while preparing food in the kitchen, to uncooked meat foodstuffs containing toxoplasma tissue cysts. If these reasons are valid, one would expect to find that boys were infected (as distinct from developing clinical manifestations) more frequently than girls and women more frequently than men. Many serological surveys have been made and while in all of them the prevalence of infection was similar in both sexes, in only a few of them were sufficient children tested to allow a comparison of boys and girls. Gibson, Eyles, Coleman & Smith (1956) found no significant difference between the prevalence in boys and girls in Tennessee as did Fleck (1965) in the children from Tristan da Cunha. Remington *et al.* (1970) found a slightly higher prevalence in males aged 6 months to 15 years than in females in El Salvador but the difference was not significant at 0·05; in a later survey in Ghana (Godwin & Remington, 1973) the prevalence was found not to differ significantly between male and female children. Grönroos (1955) found a slightly higher prevalence in girls than boys in Finland. The dye test was used in each of these five series.

It is believed that the great majority of taxoplasma infections in man are

symptomless and that these account for the positive reactions found in serological surveys. Manifestations may occur which are not recognized as being due to toxoplasmosis or which are minor and resolve so quickly that they are never investigated. We know of several conversions from sero-negative to sero-positive among our staff which were unaccompanied by ill health. One of us (D.G.F.) searched himself thoroughly and repeatedly for lymph node involvement at the time of his sero-conversion and found none.

If the prevalence of infection is the same in both sexes at all ages, then some other factor or factors must account for the differences in the frequency with which toxoplasmic lymphadenopathy is seen by medical practitioners in the two sexes at different ages. It is well known that the care of baby boys is more solicitous than that of girls. This might be exemplified by the greater number of emergency calls to sick boys than to sick girls and the larger number of sera from boys which are sent for examination. However, these differences are not so great as to account for a 1·0 to 0·22 male to female ratio of toxoplasmic lymphadenopathy in children under 5 years of age (Table 3). Of the adults with toxoplasmic lymphadenopathy, women are seen more frequently than men. Lymphadenopathy occurs most often in the neck and so may be more readily noticeable in women on account of the difference in clothing, more frequent attention to hair or for cosmetic reasons. Women are more 'lump conscious' due to an instilled awareness of the importance of early recognition and treatment of neoplastic conditions. How much these facts account for the higher frequency of toxoplasmic lymphadenopathy in women is conjectural. A pointer is the observation of Saxén *et al.* (1962) that in a series of 866 lymph node biopsies, there were 22 patients with toxoplasmosis and of these 19 were women. In the lymphadenopathies due to other causes (844) the sexes were affected equally.

In toxoplasmic lymphadenopathy, organisms can be isolated from the enlarged nodes but they are so scanty that they are rarely seen on histological examination. The enlargement of the node is not a direct result of infection in the node. It is a reactive hyperplasia. In other words it is an immunological response to infection mainly at sites other than lymph nodes. From what has been said earlier, lymphadenopathy is not a usual finding in toxoplasma infections; most infections are subclinical. The small proportion of individuals whose infections progress to lymphadenopathy may therefore be those who for some as yet unknown reason develop an exaggerated immunologically based reaction. In this connexion it should be mentioned that the other causes of lymphadenopathy in the series of Saxén *et al.* (1962) were tuberculosis, other specific inflammations, non-specific inflammations, malignant lymphogranulomatosis, other malignant lymphomas and metastatic tumours. In none of these diseases can the pathological change be described as reactive hyperplasia.

It is also of interest that in one of the British centres 9 children under 5 years were seen – 7 boys and 2 girls. Both of these girls were found to have lymphadenopathy only when they were examined, as contacts, after their brothers had been shown to have toxoplasmic lymphadenopathy. The girls' nodes were much smaller than the boys'.

Choroido-retinitis due to toxoplasmosis is thought to be the result of congenital infection in the great majority of patients. In later life, exacerbations are prone to occur and these are immunologically mediated. Nutt & Beverley (1963) observed this to occur in 30 of 78 patients (40 females and 38 males). In those aged 15–24 years, 4 males and 5 females had exacerbations. At older ages, 7 males and 14 females were so affected. These ratios are similar to those for the same age groups affected with toxoplasmic lymphadenopathy.

DISCUSSION ON OTHER DISEASES

Some of these are thought to be immunologically mediated. Even while the precise immunological mechanisms are not yet fully understood, it seems that they may well be different in different diseases.

Subacute sclerosing panencephalitis is considered to be a complication of measles which becomes apparent only after a long delay, usually of several years. The pathogenesis is not fully understood but it seems that there is an abnormal response to the virus which has persisted in the central nervous system.

The delay between parotitis and mumps encephalitis is much shorter, 7–10 days, and is comparable with that in other post-infection encephalitides. In some patients parotitis may follow the encephalitis while in others it may never be clinically manifest. The pathogenesis is still obscure but at present the most widely held belief is that it is an allergic or autoimmune phenomenon.

Adenovirus infections of types 1, 2 and 5 may cause hyperplasia of the lymphoid tissue in the ileal mucosa, particularly that around the ileocaecal valve. This may become so prominent that it acts as the apex of an intussusception in young children (Potter & Zachary, 1964).

In thyrotoxicosis, Hashimoto's disease and primary biliary cirrhosis, lymphocytic infiltration, with or without follicle formation, is a prominent part of the pathological change. Both lymphocytic infiltration and follicle formation indicate immunological activity; the former is associated with cellular immunity, the latter with humoral. Plasma cells are often seen.

It is generally accepted that there is a large immunological element in collagen and autoimmune diseases such as disseminate lupus erythematosus, myasthenia gravis, rheumatoid arthritis and haemolytic anaemias. It could be that these diseases are expressions of an unusual ability to detect and react to autologous antigens which have been modified in some way, possibly by infection, but modified so slightly that the change is not recognized by most individuals. Alternatively, those individuals who develop autoimmune diseases may have antigens which are more readily modified than those of most people.

Hodgkin's disease is considered to be primarily a tumour of reticulum cells. The other commonly seen elements constitute an immunological response to the tumour and may lead to fibrosis. The greater the response the better is the prognosis. A comparable situation is that the greater the lymphocytic infiltration, the better is the prognosis in carcinoma of the breast.

At present there is no clear indication that an immunological mechanism is

involved in the pathogenesis of cot deaths, congenital pyloric stenosis, adenovirus type 7 infections, acute hepatitis B infections or severe rhinovirus infections.

Findings in experimental animals

Differences in the susceptibility of the two sexes have been observed in some experimental protozoan infections. Hauschka (1947) found that in female mice infected with *Trypanosoma cruzi* the degree of parasitaemia was only half of that in males. This difference was maintained throughout the 11-day observation period. Only half the number of parasites was seen in the tissues of females when compared with males. Females survived longer. Goble (1966) confirmed that *T. cruzi* affected male mice more severely than females and showed that treatment with the opposite sex hormones, even to juveniles, did not affect the course of the infection. He also found greater resistance in female mice to infection with *Babesia rodhaini* and that female golden hamsters survived longer and showed less oedema following infection with *Leishmania donovani*. Gross (1941) found that tumour takes of sarcoma 37 were higher in male mice than in females and that tumour regressions occurred more frequently in females. On the other hand, Yohn, Funk, Kalnins & Grace (1965) found that male hamsters were more resistant to neonatal adenovirus-12 oncogenesis than females and that thymectomy at the age of 3 weeks enhanced the susceptibility of males to the same degree as in females while it did not enhance the susceptibility of females. Later (Yohn, Funk & Grace, 1968) they showed that thymectomy at the age of one week enhanced the susceptibility of both sexes.

Petty & Steward (1972) have shown that the antibody response of NZB/WF1 male mice to injections of human serum transferrin when measured 2 weeks after the last injection was about the same, whether immunization was started as early as 8 weeks old or as late as 26 weeks. By contrast, females had a high response at 8 weeks and progressively less when immunization was started at 12, 16 and 26 weeks. The responses of the females at 8 weeks were higher than those of the males, at 12 weeks they were equal while at 26 weeks the female response was only one-fifth of that of the males. They also found that the affinity of the antibody for antigen was greater the older the animal at the time of immunization, but the increase of affinity was much more in females than in males.

Variations in the immunological responses by man

Purtillo, Hallgren & Yunis (1972) have noted that during pregnancy there is a depression of lymphocyte transformation by plant mitogens while St Hill, Finn & Denye (1973) have shown that the depression of phytohaemagglutinin-induced lymphocyte transformation during pregnancy is dependent on a serum factor. Barnes *et al.* (1974) have found depression of lymphocyte transformation as a result of taking contraceptive pills.

Simpson, Gray & Beck (1975) have reported more marked age involution of the thymus in normal women from the age of 17 years to 37 years than in men; thereafter there was no difference between the sexes.

Conclusions

There are thus pointers to there being several diseases affecting mainly the young, and males more than females, and to there being a second group affecting mainly adults, and females more than males. Toxoplasmic lymphadenopathy could be claimed to belong to both of these groups. The former group of diseases may be a contributory factor to the higher death rates in male infants and children than in females.

The second group demonstrates the known tendency for women to be more prone to immunologically mediated disease. The observations on the varying immunological responses of women and the sex differences in thymic involution are in keeping with the belief that modifications of the immune processes occur during the child-bearing age. These may be designed to lessen the possibility of 'graft rejection' of an implanted fetus.

There are other diseases which do not fit in with either of these two groups yet which affect one sex more than the other at all ages.

While there is evidence of an immunological factor in many of the diseases discussed, in some of them there is also a familial tendency as in rheumatoid arthritis. It may be that in some of these patients there is an inherited 'defect' in some part of the immune mechanisms, possibly the possession of certain tissue antigens. So, at the present time, it would be unwise to attempt a unifying hypothesis explaining all the known differences in the sex incidence of diseases.

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