Table 1: The effect of age on NK cell number

Age(yrs)	N =	Mean NK cell μl/blood (+/- SD)	Mean NK cells % of lymphocytes (+/-SD)
20–40	25	194.9 (+/- 140.4)	9.25 (+/- 6.1)
40–60	23	187.6 (+/- 144.5)	10.59 (+/- 7.5)
> 60	67	205.8 (+/- 184.0)	11.22 (+/- 9.1)

Statistical analysis was carried out as described in the Methods; no significant differences between groups were found.

The effect of age on CD56^{dim} NK cell number: cell number remains constant with age

The influence of age on peripheral blood CD56^{dim} NK cells revealed relatively consistent numbers at all ages. A trend towards a slight increase in CD56^{dim} NK cells μl/blood was found between the 40–60 and 60+ year cohorts although this did not reach statistical significance (figure 3). A non-significant increase in CD56^{dim} NK cells as a percentage of the peripheral blood lymphoid pool was also observed with advancing age (table 2 , figure 4).

Discussion

The decline in immune function with increasing age is termed immune senescence and leads to impaired responses to vaccination, an increased incidence of autoimmune disorders and increased morbidity and mortality to infectious disease [12-15]. Immune senescence has been attributed to a number of factors including thymic involution and memory T cell accumulation resulting in contraction of the T cell repertoire. More recently, debate has focused on the role of innate cellular immunity with regard to impaired immune function. Remarque *et al*. have reported that elderly individuals with low NK numbers have a three-fold increased risk of mortality in the first two years of follow up compared to those with high NK cells [16]. Functional studies have measured NK cell activity against the K562 tumour cell line and demonstrate impaired NK cell cytotoxicity in elderly donors [17]. Further evidence is derived from studies on centenarians, regarded as a model example of healthy ageing, who have been reported to have well preserved NK cell cytotoxicity [18]. Our data shows that NK cell numbers are relatively stable with advancing age but as the total peripheral blood lymphocyte count decreases there is a small increase in the proportion of the lymphoid compartment occupied by NK cells.

Our findings demonstrate that the number of CD56^{bright} NK cells declines with advancing age which may have considerable implications for NK cell function in the elderly cohort. This decline was apparent across all three age groups indicating a gradual decline with healthy ageing. The CD56^{dim} NK cell subset remains relatively constant but occupies a greater portion of the peripheral blood lymphoid pool with advancing age. Our findings are in keeping with Krishnaraj (1997) who also reports a significant reduction in the proportion of CD56^{bright} cells with relative sparing of the CD56^{dim} subset [19]. This contrasts with Borrego *et al*. (1999) who reports an expansion in the proportion in CD56^{dim} cells but little change in CD56^{bright} NK cells [20]. Differences in the methodology employed in these studies are likely to account for the variation in results.

NK cell associated cytotoxic function is thought to be mediated primarily through the CD56^{dim} NK cell subset whereas the CD56^{bright} NK cells can be thought of primarily as a cytokine producing subset. The CD56^{dim} cell is more cytotoxic than the CD56^{bright} NK cell subset [21] and the morphological appearance of CD56^{dim} cells shows greater granularity [1]. A substantial body of data indicates that the CD56^{bright} subpopulation plays a critical role in the early innate immune response. CD56^{bright} NK cells have a higher proliferative capacity than CD56^{dim} NK cells

Table 2: The effect of age on CD56^{bright} and CD56^{dim} NK cells

Age	20–40	40–60	60+
N =	25	23	67
CD56^{bright} μl/blood (+/- SD)	15.64 (+/-12.8)	12.81 (+/-12) ***	8.13 (+/-7.9)****
CD56^{bright} as % of lymphocytes (+/-SD)	0.76 (+/-0.6)	0.72 (+/-0.6) *	0.50 (+/-0.5) **
CD56^{dim} μl/blood (+/-SD)	179.3 (+/-135.3)	174.8 (+/-135)	197.7(+/-180.3)
CD56^{dim} as % of lymphocytes (+/-SD)	8.49 (+/-5.8)	9.86 (+/-7.0)	11.7 (+/-9.3)

Statistical analysis was carried out as described in the Methods; * p = 0.031 between the 40–60 and 60+ age groups, ** p = 0.012 between the 20–40 and 60+ age groups. ***p = 0.03 between the 40–60 and 60+ age groups, ****p = 0.0004 between the 20–40 and 60+ age groups.