had a blood urea level above 6·6 mmol/l (40 mg/100 ml) and could be said to have a more than mild degree of renal impairment. The important renal factor in this study was renal tubular dysfunction, as shown by changes in the plasma urate levels. The hyperuricaemia of pre-eclampsia is due to diminished renal tubular excretion and not to excessive production (Chesley and Williams, 1945), and possibly this is due to lactic acidosis caused by anaerobic metabolism in the placenta (Handler, 1960). How prolactin and uric acid metabolism may be linked has yet to be determined, but the possibility that the link is a direct one, in that prolactin may control or modulate uric acid metabolism or excretion during pregnancy, should be considered.

Alternatively, pre-eclampsia may in some way interfere with prolactin clearance. If prolactin is cleared by the kidney, as are some other peptide hormones, then the early involvement of the kidney in pre-eclampsia as measured by plasma urate changes may also indicate a reduced prolactin clearance. Growth hormone (GH), however, which is structurally closely similar to prolactin, is thought to be cleared by the liver, at least in non-pregnant people (Taylor et al., 1972); and the liver is not known to be involved in the early development of pre-eclampsia.

Of the other endocrine changes in pre-eclampsia the reduction in circulating plasma oestrogens (Masson, 1973) provides no explanation of the increased prolactin levels, since plasma oestrogens potentiate prolactin release (Frantz et al., 1972). Human placental lactogen may also be reduced in pre-eclampsia (Letchworth and Chard, 1972) but its relation to prolactin is not known. The levels of adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH), thought to be of pituitary and not placental origin, are raised in pre-eclampsia (Genazzani et al., 1971; Mukherjee and Swyer, 1972). The same may be true of GH, but this is less certain because of the difficulty of its measurement in pregnancy (Laron et al., 1967). That prolactin is also increased gives further evidence that anterior pituitary function may be generally disturbed in pre-eclampsia. TSH and prolactin are both secreted in response to thyrotrophin-releasing hormone (Bowers et al., 1971), and the release of GH and ACTH are also under hypothalamic control. The results suggest that hypothalamic function could be disturbed in pre-eclampsia, and this seems the most likely explanation of these observations.

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Normal Haematological Values: Sex Difference in Neutrophil Count

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Summary

Blood counts were performed on 100 male and 100 female staff to establish normal ranges for our hospital. Neutrophil counts were found to be on average 0·66 × 10⁹/l (660/mm³) higher in women than in men. Statistically this difference was highly significant and was not due to the fact that many of the women were taking oral contraceptives. The neutrophil counts of the men and women were also on average 0·50 × 10⁹/l (500/mm³) greater in the afternoon than in the morning. A correlation was observed between the neutrophil and the monocyte counts.

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Introduction

Patients with absolute neutrophil counts of less than 2·5 × 10⁹/l

(2500/mm³) are often referred to haematology departments for investigation of neutropenia. It is difficult to interpret such results when the published lower limits of normal vary from as low as $1 \times 10^9/l$ (1000/mm³) to as high as $3 \times 10^9/l$ (3000/mm³) (Osgood et al., 1939; Engelbreth-Holm and Videbaek, 1948; Zarofonetis, 1952; Dacie and Lewis, 1968; Orfanakis et al., 1970; Zacharski et al., 1971). We therefore decided to establish our own normal ranges, performing 500-cell differential counts and using the automated techniques which are now widely used for determining the total white cell count.

Methods

Venous blood samples were obtained from 100 male and 100 female hospital staff of European origin, aged between 18 and 60 years with median ages of 24 for the men and 25 for the women. Pregnant women, blood donors, and those with coughs, colds, and other minor infections were excluded though three postmenopausal women were included. Venepunctures were performed throughout the year. Altogether 72 men and 70 women were bled between 9.30 and 11.30 a.m., 26 men and 29 women between 2.30 and 4.30 p.m., and two men and one woman after 5 p.m. These times were selected for investigation as they are the times at which blood samples are usually obtained from hospital inpatients and outpatients. Venepunctures were not performed immediately after eating or after any unusual exertion.

The blood samples were anticoagulated with K_2 adetic acid, and counted on a Coulter counter, Model S, standardized with 4C Coulter counter cell control. Romanowsky-stained blood films were prepared and differential counts were performed on 500 cells, counting in longitudinal strips. All the counts were made by one observer.

STATISTICAL ANALYSIS

Total leucocyte count and absolute neutrophil, lymphocyte, and monocyte counts were found to be log normally distributed: a straight line was obtained when the cumulative frequency was plotted on a probability scale against the count on a logarithmic scale (fig. 1) (Healy, 1968). When eosinophil counts were plotted in this manner a curve was obtained with an upward concavity, but by using the method of Kapteyn (Gaddum, 1945) we found that the eosinophil count plus 16 gave a log normal distribution (fig. 1). By calculating the mean (μ) and the S.D. (σ) of the logarithms of the counts the median count (exp (μ)) and the 95% confidence limits (exp (μ) ± 1.96σ) for the counts were derived. Sixteen was then subtracted from the median value and the confidence limits calculated for the eosinophil counts.

In many of the subjects the absolute basophil count was apparently zero because no basophils were seen in the 500-cell differential. It was therefore necessary to use the observed 50th percentile as the median and the 2·5 and 97·5 percentiles as the 95% confidence limits because no simple transformation would convert the basophil counts to a normal distribution.
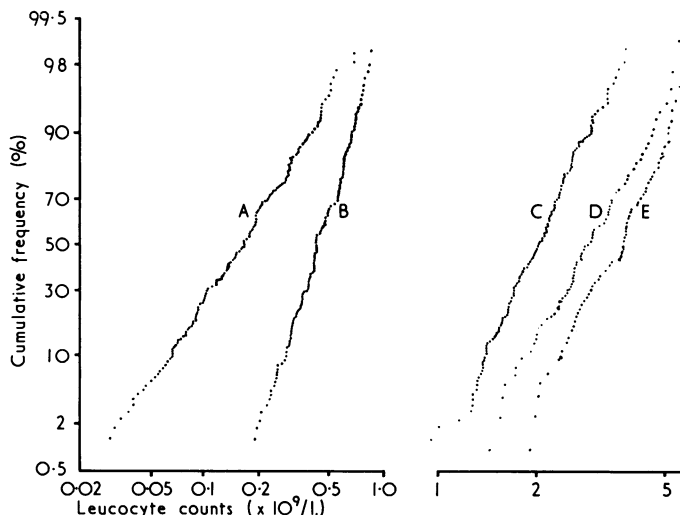

FIG. 1—Leucocyte counts. Cumulative frequencies plotted on probability scale against leucocyte counts on logarithmic scales. A = Eosinophil counts +16. B = Monocyte counts. C = Lymphocyte counts. D = Neutrophil counts in men (9.30x11.30 a.m.). E = Neutrophil counts in women (9.30-11.30 a.m.) Conversion: SI to Traditional Units—Leucocytes: $1 \times 10^9/l = 1000/mm^3$.

The values of μ and σ^2 for different groups were compared using Student's t test and the F test respectively. An analysis of variance was used to compare the male and female values in the morning and the afternoon and to compare the morning and afternoon values in women taking or not taking oral contraceptives. For correlation analysis and analysis of variance the logarithms of the counts were used.

We also reanalysed the results of Osgood et al. (1939) to compare with our own. Their total leucocyte count and absolute neutrophil and lymphocyte counts were log normally distributed, and 95% confidence limits were computed as above. For the absolute monocyte, eosinophil, and basophil counts many zero counts were recorded and it was necessary to use the observed 2·5 and 97·5 percentiles as the 95% confidence limits.

Results

NORMAL VALUES

The total leucocyte count was significantly higher in women than in men (P <0·001) due to a highly significant difference in the neutrophil counts (P <0·0001; table I). In both sexes the total leucocyte count and the neutrophil count were also significantly higher in the afternoon than in the morning (P <0·05). The 95% confidence limits for the neutrophil counts in women and men were, respectively, $1·861 \times 10^9$–$6·821 \times 10^9/l$ (1861–6821/mm³) and $1·539 \times 10^9$–$5·641 \times 10^9/l$ (1539–5641/mm³) in the morning and in the afternoon $2·137 \times 10^9$–$7·836 \times 10^9/l$ (2137–7836/mm³) and $1·775 \times 10^9$–$6·508 \times 10^9/l$ (1775–6508/mm³) (table II). The lower values found for the men imply, for example, that four and a half times as many

TABLE I—Median Leucocyte Counts in Male and Female Hospital Staff in Morning (9.30-11.30 a.m.) and Afternoon (2.30-4.30 p.m.)

| | Men | | Women | | | | | |
| | | | Morning | | | Afternoon | | |
	Morning	Afternoon	All Women	Women on Oral Contraceptives	Women Not on Oral Contraceptives	All Women	Women on Oral Contraceptives	Women Not on Oral Contraceptives
Total leucocytes (× 10⁹/l)	5·665	6·049	6·237	6·365	6·215	7·231	7·260	7·380
Neutrophils (× 10⁹/l)	2·952	3·400	3·563	3·668	3·597	4·093	4·122	4·311
Lymphocytes (× 10⁹/l)	1·956	1·868	1·969	2·001	1·918	2·283	2·324	2·199
Monocytes (× 10⁹/l)	0·427	0·434	0·416	0·390	0·424	0·481	0·461	0·497
Eosinophils (× 10⁹/l)	0·150	0·156	0·122	0·130	0·126	0·151	0·152	0·151
Basophils (× 10⁹/l)	0·035	0·040	0·025	0·026	0·023	0·048	0·048	0·046

Conversion: SI to Traditional Units—W.B.C.: $1 \times 10^9/l = 1000/mm^3$.

TABLE II—*Normal Values in 100 Male and 100 Female Hospital Staff. 95% Confidence Limits. Values for Both Sexes Combined are given in Parentheses where Appropriate*

	Men	Women
Total leucocytes (× 10⁹/l):*		
Morning	3·487–9·206	3·839–1·0135
Afternoon	3·722–9·828	4·450–1·1750
Neutrophils (× 10⁹/l):*		
Morning	1·539–5·641	1·861–6·821
Afternoon	1·775–6·508	2·137–7·836
Lymphocytes (× 10⁹/l)*	1·168–3·262 (1·158–3·460)	1·149–3·664
Monocytes (× 10⁹/l)*	0·217–0·849 (0·221–0·843)	0·225–0·836
Eosinophils (× 10⁹/l)†	0·030–0·592 (0·025–0·0590)	0·020–0·582
Basophils (× 10⁹/l):‡		
Morning	0–0·131	0–0·138
Afternoon	0–0·120	0–0·141
Red cell count (× 10¹² /l)	4·28–5·49	3.86–4·94
Haemoglobin (g/dl)	13·1–16·5	12·0–14·7
Packed cell volume	0·384–0·490	0·358–0·435
Mean corpuscular volume (fl.)	81·9–96·5 (82·0–97·1)	82·3–97·7
Mean corpuscular haemoglobin (pg)	27·8–32·6 (27·7–32·9)	27·7–33·2
Mean corpuscular haemoglobin concentration (g/dl)	31·9–35·9 (32·1–35·5)	32·2–35·2

*Lognormal distribution.
†Lognormal distribution of count plus 16.
‡Observed percentiles.

Conversion: SI to Traditional Units W.B.C.: 1 × 10⁹/ = 1000/mm³.t

men as women have neutrophil counts below $2 \times 10^9/l$ (2000/mm³) in the morning; similarly, over twice as many women have counts above $5 \times 10^9/l$ (5000/mm³) (fig. 2).

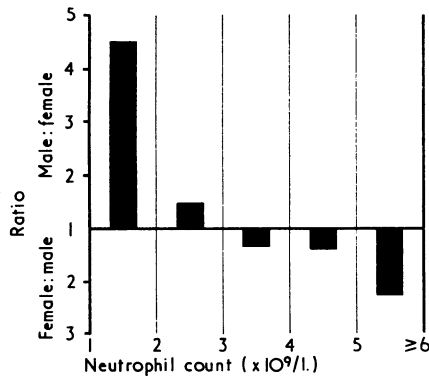No significant differences were found between the absolute

FIG. 2—Neutrophil counts. Relative frequency with which various counts were observed in men and women. When counts were commoner in men than women the results are presented as male : female ratio and when reverse was true results are presented as female : male ratio. All values are for 9.30-11.30 a.m.
Conversion: SI to Traditional Units—Neutrophils: 1 × 10⁹/l = 1000 mm³.

lymphocyte, monocyte, and eosinophil counts of the men and the women nor were there any differences between the morning and the afternoon (P > 0·05; table I). The women, however, had higher basophil counts in the afternoon than in the morning (table I)—for example, 21% of women had counts above $0·06 \times 10^9/l$ (60/mm³) in the morning and 45% had similar counts in the afternoon (P < 0·05, χ^2 test). The 95% confidence limits for these counts are given in table II.

ORAL CONTRACEPTIVES

Since many of the women were taking oral contraceptives,

which have been reported to raise the neutrophil count (Pincus, 1965), we decided to compare the haematological values of those premenopausal women taking oral contraceptives with the values of those who were not. No significant differences were observed between the two groups for the neutrophil count or for any other measurement either in the morning or in the afternoon (P > 0·05) though in both groups the neutrophil counts were higher in the afternoon (table I).

The neutrophil counts of the women taking oral contraceptives were significantly higher than those of the men (P < 0·005), as were the counts of the women not taking oral contraceptives (P < 0·001).

CORRELATION BETWEEN NEUTROPHIL AND MONOCYTE COUNTS

In both women and men there were significant correlations between the neutrophil and the monocyte counts in both the morning and the afternoon (women in the morning r = 0·431, P < 0·001; women in the afternoon r = 0·470, P < 0·05; men in the morning r = 0·274, P < 0·05; men in the afternoon r = 0·628, P < 0·001). This correlation, while being of great theoretical interest, explains only a small part of the observed variation in the monocyte count. No statistically significant correlations were found between the absolute counts of any other two white cell types.

Discussion

We observed a higher total leucocyte count in women than in men due to a highly significant difference in the absolute neutrophil count. Several workers have previously investigated leucocyte counts in men and women. One of the earliest studies was that of Osgood et al. (1939), who observed that women had a slightly higher neutrophil count than men but that the observed difference was not statistically significant (table III). Since then Heine et al. (1960) have reported that women have higher neutrophil counts than men, but Allan and Alexander (1968) claimed that women had significantly lower counts. Other workers have not related their results to the sex of their subjects or have studied subjects predominantly of one sex (Turner, 1956; Wintrobe, 1967; Orfanakis et al., 1970).

There are several possible explanations for the difference in neutrophil counts between men and women. MacKinnon (1953) and Morley (1966) have suggested that there is a cyclical variation of the neutrophil count with the menstrual cycle. These findings imply that the level of oestrogen or progestogen may be an important factor in regulating the neutrophil count. A rise of the neutrophil count is also associated with increasing hormone levels in pregnancy. Furthermore, oestrogen levels correlate with the neutrophil count in women treated with follicle-stimulating hormone and chorionic gonadotrophin (Cruickshank et al., 1970), and oestrogen seems to enhance granulocyte proliferation in vitro (Reisner, 1966). Our small number of postmenopausal women did not differ from the rest of the female group but studies of larger groups of postmenopausal women have shown a postmenopausal fall in the neutrophil count (Allan and Alexander, 1968; Cruickshank and Alexander, 1970).

The difference in neutrophil counts between the men and the women was unrelated to oral contraceptive therapy; those

TABLE III—*Normal Values for Leucocytes: 95% Confidence Limits reported in Previous Studies*

	No. of Subjects	Total Leucocytes (× 10⁹/l)	Neutrophils (× 10⁹/l)	Lymphocytes (× 10⁹/l)	Monocytes (× 10⁹/l)	Eosinophils (× 10⁹/l)	Basophils (× 10⁹/l)
Osgood et al., 1939* {	198 M.	4·637–1·0965	1·913–7·356	} 1·300–5·169	0–0·870	0–0·600	0–0·190
	71 F.	4·509–1·1666	1·945–8·239				
Blackburn et al., 1947	642 M.	4·148–12·130	1·815–8·056	1·308–4·818	0–0·852	0–0·469	0–0·272
Orfanakis et al., 1970	204 M., 22 F.	4·550–10·100	2·050–6·800	1·500–4·000	0·220–0·950	0·030–0·860	0–0·160
Zacharski et al., 1971	292 M., 215 F.	4·100–10·900	2·266–7·676	0·832–3·140	0·123–0·804	0–0·492	0–0·156

*See Statistical Analysis.   *Conversion: SI to Traditional Units*—W.B.C.: 1 × 10⁹/l = 1000/mm³.

women who were taking oral contraceptives did not have a higher neutrophil count than those who were not and both groups had counts which were significantly higher than those of the men. Our observations contrast with those of Pincus (1965), who showed that oral contraceptives raised the neutrophil count. His subjects were taking preparations with 75–150 μg of oestrogen, however, whereas the oral contraceptives taken by our subjects contained 30–50 μg of oestrogen and also usually had a lower progestogen content.

Our results also confirm earlier observations that the neutrophil count rises in the afternoon (Garrey and Bryan, 1935; Kennon et al., 1937). We therefore suggest that it is important to consider both the sex and the time of day when deciding whether a neutrophil count is lower than normal. The lower limit of normal which is widely used is 2.5×10^9 neutrophils/l (2500/mm³). Our results show that this value is too high for either sex, particularly in the morning, when—for example, 31% of our normal men had counts below this level.

Variation of the neutrophil count may also occur on a racial basis. For example, Shaper and Lewis (1971) have observed a mean neutrophil count of $1.96 \times 10^9/l$ (1960/mm³) in 250 male African blood donors. This value is lower than the mean value which we found in this study of Caucasians of European origin.

The values we have observed for the lymphocyte, monocyte, eosinophil, and basophil counts are similar to those in previously published series (table III), and we have also confirmed earlier observations that the basophil count rises in the afternoon (Finch, 1972). The correlation which we have noted between the monocyte and the neutrophil count was previously reported by Twomey et al. (1973). This interesting correlation is consistent with the suggestions that neutrophils and monocytes either have a common precursor or have similar regulatory mechanisms.

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Postoperative Management after Thymectomy

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Summary

This paper reports a retrospective study of the preoperative and postoperative management of 28 patients who underwent thymectomy between 1956 and 1973. Patients who received postoperative artificial ventilation were compared with the group who did not with respect to sex, age, severity of disease, preoperative vital capacity, and thymic histology. Evidence is presented that postoperative artificial ventilation is required when the preoperative vital capacity with the patient on optimum anticholinesterase treatment is less than 2 litres. Additional features associated with a probable need for artificial ventilation were the presence of a thymoma, bulbar symptoms, especially dysphagia, and age over 50 years. These should be taken into account in any patient whose vital capacity is close to the critical level of 2 litres. When postoperative ventilation was required it was usually necessary for 12 days or more, and tracheostomy should therefore be done at or before thymectomy. Most patients in this series received the same dose of anticholinesterases after operation as before it and no evidence was found of a sudden decrease in requirements for anticholinesterase therapy. Two patients did not, and in them a myasthenic crisis was precipitated. We propose that the preoperative drug regimen can be continued in the immediate postthymectomy period, allowing selection of patients for tracheostomy and artificial ventilation primarily on the basis of the preoperative vital capacity.

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Introduction

Though there is general agreement on the value of thymectomy in myasthenia gravis there is controversy about the immediate postoperative management. A postoperative mortality of 10% in the earlier years led to the adoption of regimens such as that of Osserman and Genkins (1971), who advocated routine