A STUDY OF THE MODE OF ACTION OF CYCLOPHOSPHAMIDE
AND ITS PHYSIOLOGICAL EFFECTS ON MERINO SHEEP

by

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SUMMARY

1) This thesis is concerned with the physiological effects of cyclophosphamide (CPA) in the Merino sheep, and with its mode of action.

2) Pen experiments were used to evaluate the physiological impact of CPA, and field trials were included to determine the effect of CPA defleecing on the productivity of the sheep.

3) The oral route of administration of CPA is the most practical but the smallest excreted amounts of CPA metabolites (the active material) were produced by this route. The order of increasing yield of CPA metabolites (as measured by CPA metabolites in the urine) was from oral (least), to subcutaneous, intraperitoneal, and then the greatest amount came from intravenous administration.

4) The inhibition of mitotic activity of wool follicles began within 3 hr of CPA administration, and a period of 14 days elapsed before normal rates of cell division were regained.

5) The level of feeding did not influence the rate of onset of mitotic inhibition or the recovery of mitotic activity from the effects of CPA. A high nutritional status increased the metabolite yield of orally administered CPA.

6) Oral CPA reduced the rumen protozoal populations but
rumen bacterial numbers and rumen pH were unaffected. There appeared to be very little metabolism of CPA in the rumen.

7) In normally hydrated sheep, urine flow was reduced by CPA but there were only minor alterations in glomerular filtration or electrolyte excretion and concentration.

8) There was extensive reabsorption of CPA metabolites by the kidneys.

9) When the water status of the sheep was altered, CPA acted as a mild diuretic and once again there were only minor changes to glomerular filtration and electrolyte excretion.

10) Although changed nutritional and water status altered the extent of CPA metabolism, there was very little impact on the biological effectiveness of the CPA as measured by leucocyte depression, and fleece shedding.

11) Four annual CPA defleeTINGS did not produce any changes in wool quality and quantity.

12) Four annual CPA defleeTINGS in the last trimester of pregnancy did not affect the lambs produced, as measured by growth rates and wool production. The fertility of the CPA-defleeced ewes was slightly higher than that of a conventionally shorn control group.

13) Rugging of the sheep was required from the time of
CPA administration to prevent premature loss of wool. After defleecing the rugs were needed to protect the sheep from the sun or from environmental cold.

14) The sheep developed resistance to CPA defleecing with repeated CPA administrations. No consistent changes were found in body weight, wool fibre diameter and coefficient of variation of the fibre diameter. The repeated dosings with CPA resulted in greater metabolism of orally administered CPA, but on the seventh and eighth doses of oral CPA there was a reduction in wool fibre diameter.