THE CIRCULATORY RESPONSE TO EXPERIMENTAL POST-HAEMORRHAGIC ANAEMIA.

I. DARIAN SMITH M.B., B.S..

Thesis submitted for the Degree of Doctor of Medicine at the University of Adelaide, 1955.

KANEMATSU MEMORIAL INSTITUTE OF PATHOLOGY,
SYDNEY HOSPITAL,
SYDNEY.

I N D E X.

INDEX CONTD.

I N D E X CONTD.

CHAPTER 1.

INTRODUCTION.

Anaemia may be defined as an abnormal condition in an animal where there is a deficiency of red blood cells and haemoglobin per unit of blood. This term in no way defines any change in the total volume of circulating red cells, or haemoglobin in the animal, but, in fact, this is also usually reduced. By far the most important physiological consequence of this red cell deficiency is the limiting of the amount of oxygen which may be transported, combined with haemoglobin, per unit volume of blood. The clinician has observed that even when the anaemia is gross, the patient may be only slightly inconvenienced, sound evidence that the physiological compensation for this defect may be very effective.

Very extensive investigations of this compensatory mechanism have been made, but practically every investigator has, quite naturally, concerned himself with isolated aspects of the problem. Correlation of the various findings, in order to obtain a true picture of the total circulatory response in the animal to the stress of anaemia has been difficult, for two main reasons:-

1. Most investigations have been made on anaemic patients. The difficulty arising in these investigations was due largely to the variations which occurred both within series and between the different series of patients observed. Variations, such as aetiology of the anaemia, and complicating clinical conditions made the estimation of the response to anaemia per se, very difficult. An instance of the

of the possible effect of the aetiology of the anaemia on a particular circulatory response may be cited in the quite recent literature. Bradley & Bradley (1947) reported a reduction in total renal blood flow in cases of severe pernicious anaemia. Using the same methods, Bruck (1953) recently reported an actual increase in renal blood flow in children suffer ing from Cooley's anaemia and Sickle cell anaemia. Obviously, some other factor than simply the anaemia is involved in this renal vascular response. This is discussed more fully later. The most successful clinical investigations into the problem have been those on small groups of patients suffering from a particular type of anaemia, and in which the response each patient has been observed at several haemoglobin levels, usually during clinical recovery. By this means much of the confusing uncontrolled variation has been reduced. However, few such investigations have been made, those of Richards & Strauss (1928) & Dautrebande (1925) on the cardiac response being of considerably more value than many other similar investigations because of this type of experimental design.

2. The limitations of the experimental approach using laboratory animals. The difficulty with this approach as with the experimental investigation of many chronic pathological conditions which occur inman, was the production of anaemia in suitable animals.

Nutritional anaemias, such as produced by Whipple (1935) were unsatisfactory, because although the degree of anaemia was quite sufficient for morphological or aetiological studies, the haemoglobin

concentration did not commonly fall below 7 grm.%, insufficient to produce a marked circulatory response. The various experimental haemolytic anaemias, if produced by injection of phenylhydrazin, were also unsatisfactory, because of marked side effects (dogs become clinically sick). Post haemorrhagic anaemia has been the most satisfactory experimental anaemia for this type of investigation, but frequent bleeding of the dog, the animal usually used for circulatory investigations, is not easy and other requires anaesthesia. The result has been that very limited series of anaemic dogs have been investigated.

The aim of the present investigation was to obtain a satisfactory picture of several aspects of the circulatory response to anaemia per se and to investigate the additional effects on these of certain factors which might vary in different types of anaemia, e.g. total blood volume. It was hoped that by such an approach a less confused view might be obtained of the factors influencing cardial function in this condition.

Plan of Experiments:

Dogs, the standard laboratory animal for most experimental circulatory investigations were not available, and so rabbits were used. This happened to be the greatest single technical advantage, over previous work, in the present investigation. Rabbits can be bled daily 10-20% of the total blood volume from the marginal ear vein in 5 - 10 minutes. This enabled large series of anaemic rabbits to be investigated, which allowed suitable statistical treatment of the results. Just

prior to starting this work, Dr. Paul Korner in this laboratory, had applied the direct Fick method for determining the cardiac output in unanaesthetized rabbits for studying the circulatory effects of anoxia and this method was used in the initial investigations in anaemic rabbits. Subsequently, other necessary techiques - flowmeters etc., were modified for use in unanaesthetized rabbit. Thus a wide variety of responses were observed in comparable groups of anaemic animals. The assertion by some workers that the rabbit is an unsuitable animal for this type of experiment is unfounded, as was shown by experience. However, this animal withstands poorly operative interference and prolonged general anaesthesia, and all experiments were necessarily designed to limit these factors.

Investigations were done in three phases.

1. Investigation of the cardiac output in graded anaemias and its interrelation with blood volume changes, and mean right atrial pressure changes. The time factor in the cardial response to sudden changes in haemoglobin concentration and in total blood volume was investigated.

2. Investigation of the vasomotor response in skeletal muscle to anaemia, to sudden changes in haemoglobin concentration and blood volume and the nechanism regulating the vasomotor tone changes.

3. A similar investigation of the renal vasomotor response in anaemia.

This work has been published, or is in press in the following papers:-

1. The Changes in Cardiac Output, Right Atrial Pressure, & Blood Volume in Haemorrhagic Anaemia in Unanaesthetized Rabbits.

   I. Darian Smith & W.J. Simmonds.

   Austral. J. exp. Biol. (1954): 32, pp 241 -252.

2. The Cardiac Output in Normal Unanaesthetized & Anaesthetized Rabbits.

   P.I. Korner & I. Darian Smith.

   Austral J. exp Biol. (1954): 32, pp 499-510.

3. An Analysis of Some Factors in the Cardio-vascular Response to Anaemia in the Unanaesthetized Rabbit.

   I. Darian Smith

   Austral. J. exp. Biol (1954): 32, pp 783-794.

4. The Pressure - flow Relationship in the Femoral Vascular Bed of Unanaesthetized Rabbits During Intravenous l-noradrenaline Infusions.

   I. Darian Smith

   Austral J. exp. Biol (1955): in press. (October)

5. Vasomotor Responses in the Femoral Vascular Bed to Post-haemorrhagic Anaemia in Unanaesthetized Rabbits.

   I. Darian Smith

   Austral. J. exp. Biol (1955): in press. (October)

6. The Renal Circulatory Response to Post-haemorrhagic Anaemia in Unanaesthetized Rabbits.

   I. Darian Smith

Austral J. exp. Biol (1955): to be published.

All work in these papers and in the present thesis was done by the author, except in the paper published with Dr. P.I. Korner on the normal cardiac output, when the pooling of results in normal animals was made to enable an adequate statistical analysis. This is indicated later in the thesis.