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Red Cells : Professor T. A. J. Prankerd reviews current knowledge of both the normal and abnormal structure and metabolism of the red blood cell (p. 1017).

Essential Hypertension : Sir George Pickering concludes his St. Cyres lecture on the nature and causes of hypertension, discussing the parts played by inheritance and the environment (p. 1021). Leader on this page.

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Enigma of Hypertension

As well as being important to the health and longevity of man the study of hypertension continues to be one of the most intellectually stimulating challenges. It has engaged the best brains in scientific medicine from Bright through Goldblatt to Pickering and Platt and many others too numerous to mention.

One of the merits of this problem is that it enlists the resources of several branches of medical science, thus transcending the conventional divisions of medical practice. Its pursuit starts from Poiseuille's law, which relates the velocity of flow in a tube to the cross-section of it, and spreads through neurovascular physiology, endocrinology, nephrology, psychology, and the most sophisticated techniques of statistics and genetics. This fundamental approach is admirably illustrated in Sir George Pickering's St. Cyres lecture, which has appeared in two parts in this and the preceding number of the *B.M.J.*

Much of the lecture is devoted to an exposition of the concept that, apart from certain well-defined diseases such as nephritis and phaeochromocytoma, the level of a person's blood-pressure is a quantitative characteristic determined by a variety of factors just as stature is. This hypothesis has a profound biological significance. It implies that there is no sharp distinction between the normal and abnormal, but a continuous gradation from the well-adapted to the ill-adapted. Clinical medicine has been somewhat slow to adopt this outlook. Perfect health—that is, complete adaptation—is a philosophical abstraction. Individuals in virtue of their particular physical and chemical characteristics are more or less fitted to function and survive. Just as excessive stature carries with it certain physical risks so excessive blood-pressure carries physical hazards.

The controversy between Pickering and Platt on the nature of essential hypertension has proved one of the most stimulating and illuminating debates in the history of the subject. Conducted as it has been by two friends anxious only to get to the root of the matter and not merely to score debating points, it has happily lacked the polemics and abuse that marred the scientific debates of the last century. Quite apart from the problem itself, a study of the debate has been educationally beneficial to many students of medicine both young and old.

Pickering summarizes the steps in the controversy. In brief, Platt maintains that in the causation of essential hypertension there are one, or at the most two or three, distinct inherited characteristics. Pickering, on the other hand, believes that blood-pressure is a characteristic determined by the summation of many factors both inherited and environmental. The basic test to which these conflicting hypotheses have to be submitted is the frequency distribution. If a multiplicity of factors determine the level of blood-pressure, then the graph of its frequency in any sample of a population sufficiently large to be representative of the whole should fall along a Gaussian curve. This is the curve of a distribution determined by many factors none of which dominate. On

the other hand, if the curve of the frequency distribution does not assume this form but has two or more peaks, then one or more dominant factors are at work. In theory the problem is simple. Thereafter it resolves itself into the acquisition of enough accurate measurements of blood-pressure in a sample of people representative of the whole population.

Pickering's review of the evidence suggests strongly that the level of blood-pressure is "normally" distributed—that is, no one factor is a dominant cause. Any distortions noted are considered to be due to the preference for certain digits that people who must make many measurements often show. In fact, the evidence for multiple causation seems to be as good for blood-pressure as it does for stature.

Platt claims that data on the blood-pressure of siblings of patients with essential hypertension, when displayed as a frequency distribution, suggest that essential hypertension is due to an inherited dominant gene. This conclusion has been criticized on the argument that the bimodality of the curve is due to the effect of digit preference by the observers. More recently Platt has studied a group of relatives of hypertensive patients and claims that the shape of the distribution curves of their blood-pressures suggests there are three groups distinguished by mode of inheritance of factors causing hypertension. These conclusions have been criticized as being based on insufficiently large numbers.

So far the weight of evidence seems to favour the multifactorial hypothesis of Pickering, but students of clinical science should not accept the opinion of reviewers: they should study the data for themselves. Fortunately this is possible, because the principal publications in this field include the "raw" numerical data, enabling the reader to make his own statistical analysis and draw his own conclusions. This is as it should be and does credit to the editorial policy of the journals concerned, particularly *Clinical Science*. Scientific reports should describe the methods of observation and experiment and give the results in such detail as to enable others to repeat the work or to fit the data into some other hypothesis. Numerical data fully reported are eternal, while discussion and debate are contemporary and ephemeral.

It must not be thought that this controversy is a purely academic affair of little concern to the practising clinician, for the opposing hypotheses differ fundamentally on the causation of essential hypertension. The view that one or more dominant inherited factors are creating a distinct "abnormal" population of hypertensives implies the need to concentrate on genetic studies and on possible ways of controlling the effects of such inheritance. The multifactorial hypothesis, on the other hand, offers wide scope for the detection of the many environmental factors promoting the higher values of blood-pressure.

Pickering summarizes the results of the statistical analysis by W. E. Miall and P. D. Oldham[1] of their blood-pressure readings in a large sample of first-degree relatives living in the Rhondda Fach and the Vale of Glamorgan. These point strongly to the inheritance of blood-pressure quantitatively as a graded characteristic, and the analysis suggests that about two-thirds of the variance is due to non-familial environmental factors. Some of these factors are known already—such as obesity, physical work, and family size. The recognition of others is the opportunity of the clinician, particularly the family doctor, who is prepared to measure blood-pressure, take weights, keep records, keep an open mind, and use his wits.

[1] Miall, W. E., and Oldham, P. D., *Brit. med. J.*, 1963, **1**, 75.

Intravenous Iron

The introduction of parenteral iron preparations that were effective and safe was a considerable advance which made possible the treatment of patients who were refractory to iron given by mouth. The first practical solution was a preparation of saccharated iron used by J. A. Nissim[1] in 1947; he gave fairly large doses ranging up to 500 mg. of iron in one infusion. In 1949 H. G. B. Slack and J. F. Wilkinson,[2] working in Manchester, published details of a 2% saccharated iron solution suitable for manufacture on a commercial scale which was called Ferrivenin; the recommended dose was 25 mg. of iron for every deficit of 1% (0.148 g./100 ml.) haemoglobin, and they preferred to give this in divided doses working up from a test dose of 25 mg. to as many doses of 200 mg. iron in 10 ml. solution as were necessary. They also tried single infusions of 500 ml. iron, but the patients had troublesome reactions. In 1954 I. M. Baird and D. A. Podmore,[3] in Sheffield, introduced a solution of iron and dextran designed for intramuscular injection known as Imferon; it was a 5% solution and an allowance of 43 mg. of iron for every 1% haemoglobin deficit was advised. It could also be used for intravenous administration, but it was necessary to take blood for blood-grouping before the dose was given, since the dextran interfered with correct reading of the grouping mixtures.

Treatment by a series of intravenous or intramuscular doses was sometimes difficult to arrange and in pregnancy presented the added difficulty that frequent attendance at surgery or clinic was very inconvenient, and in the later stages of pregnancy time was limited. In 1963 S. K. Basu[4] reported his experience with "total-dose Imferon." He calculated the total dose of iron needed by the patient using the formula: total dose of iron in mg. = weight in lb. × haemoglobin deficit in % × 0.3. This dose was then given in dilute solution to the patient in an intravenous drip which ran only slowly over four to six hours. The treatment could be given at a single visit to the clinic, and Basu reported no untoward results. In 1964 S. Marchasin and R. O. Wallerstein[5] described their experience with the use of undiluted iron-dextran given as a total-dose slow intravenous drip; they treated 37 patients and stated that systemic reactions occurred in only one.

This technique of giving the whole dose of iron-dextran in a single intravenous drip lasting for some hours has been widely tested. Few workers have had the untroubled experience of those who introduced it. The troubles have been due to systemic reactions, sometimes serious, and to thrombophlebitis at the site of the infusion. B. Clay and others,[6] at Hull, treated 150 maternity patients and recorded 13 systemic reactions, seven of which were sufficiently severe to need emergency treatment; all the women who had the reactions were later delivered of healthy babies. All the reactions occurred in the pregnant patients and none in the patients who had been delivered. These workers were sufficiently impressed with the severity of the reactions to abandon the technique for the treatment of anaemia in pregnancy.

At page 1030 of the *B.M.J.* this week Dr. John Bonnar, of Glasgow, gives a somewhat more favourable report. He used the total dose calculated from the formula, but for antenatal patients added 500 mg. of iron for the benefit of the foetus. The total dose was diluted to 5% in normal saline or 5% dextrose immediately before setting up the infusion. Certain other precautions were observed: the skin