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

of the arm was cleaned with ether soap and no alcohol was allowed near ; the patient was given a dose of an oral antihistamine 30 minutes before the infusion, and the infusion itself was run at only 10 drops a minute for the first 15–30 minutes, and then increased to the standard rate of 45 drops per minute if there were no systemic reactions. Bonnar treated 250 patients ; 50 were pregnant and 200 had anaemia after some post-partum complication. Only three had serious systemic reactions, and they were all among the 50 pregnant patients. Local phlebitis was troublesome. Addition of hydrocortisone and heparin to the intravenous solution did not help, but when saline was used instead of 5% dextrose reactions were at least reduced. Bonnar considers that the advantages outweigh the disadvantages, especially in the treatment of anaemia in late pregnancy, when this technique stimulates a more rapid response than other methods of administering iron. Incidentally, he discovered that such energetic treatment of iron deficiency in late pregnancy unmasked a folic-acid deficiency in 10 out of his 50 patients. This possibility must always be considered in serious antenatal anaemia, because, if it is unrecognized, the response to iron treatment will be less than expected. In the patients who were treated for post-partum anaemia Bonnar considers that similar results could have been obtained in most of them with treatment by mouth, but he points out that the response was quicker and also that many of the patients were returning to responsibilities at home which might cause them to forget their regular oral dose.

Bonnar has made out a good case for sometimes treating the anaemia of late pregnancy with intravenous iron-dextran. But as a rule the indications for giving parenteral instead of oral iron remain limited.[7] The patients who really need parenteral iron are as follows. Firstly, there is a group of patients, mostly elderly women, who fail to absorb iron or absorb it so poorly that it fails to cover daily losses. This was the group who were rescued from a life of chronic anaemia when the first successful parenteral iron preparations were introduced. If this condition is suspected, it can be detected by an iron-absorption test consisting simply in giving a therapeutic dose of a suitable iron preparation and estimating the level of iron in the serum before and three hours after the dose. In patients with normal absorption the serum-iron level will rise to several times the original figure ; in patients who absorb poorly the level will remain unchanged or hardly rise at all. These poor absorbers must be given parenteral iron and could be conveniently treated by Bonnar's technique with total-dose iron-dextran infusion. Secondly there are the patients who have malabsorption syndromes, especially steatorrhoea. Thirdly are those with anaemia in late pregnancy, because time cannot be afforded to find out whether or not they absorb oral iron satisfactorily and it is essential to improve their haemoglobin level as rapidly as possible, so avoiding the use of blood transfusion. Finally there is a small group of patients who have had chronic iron deficiency so long that their iron stores are exhausted and oral iron fails to improve the circulating haemoglobin level even though absorption is adequate ; in such patients a single "total" dose of iron-dextran will relieve the anaemia and enable further iron by mouth to keep them from relapsing.

The majority of patients with iron-deficiency anaemia can and should be treated with oral iron preparations. D. J. O'Sullivan, P. G. Higgins, and J. F. Wilkinson[8] showed that the effectiveness of the various iron salts depends on the dose of elemental iron and not on which salt is used, though they confirmed that ferric salts are much less efficient than ferrous. The different ferrous preparations now available differ in the unpleasant side-effects they produce in a proportion of patients. O'Sullivan and his colleagues found that about 13% of patients had reactions such as indigestion, vomiting, constipation, or diarrhoea, but those who had reactions with one salt were not necessarily the same as those who did with another salt. Ferrous sulphate seems rather more apt to produce side-effects than the others, but there are now many alternatives available such as ferrous gluconate, succinate, fumarate, and carbonate. The dose for all should be adjusted to give the patient 180 to 200 mg. elemental iron daily and it should be possible in most cases to find one preparation that will suit. Oral iron preparations allowing improved absorption of iron are now being produced: M. C. G. Israëls and T. A. Cook[9] have reported experience with a "slow-release" preparation of iron and a mixture with an "absorption-improver"—ferrous succinate with succinic acid. Both types of preparation improve iron-deficiency states with doses only about half those needed for the standard iron preparations, and the proportion of intolerant patients has been further reduced, though not eliminated. These new preparations together with the standard ones should enable almost every patient with iron-deficiency anaemia to be treated without recourse to parenteral iron. The only absolute indication for parenteral iron without previous trial or oral preparations is thus the occurrence of severe iron-deficiency in late pregnancy. The need of other patients for parenteral treatment will appear when they fail to respond to iron by mouth, which should, if necessary, be tried in the new preparations giving slow release and improved absorption.

[1] Nissim, J. A., *Lancet*, 1947, **2**, 49.
[2] Slack, H. G. B., and Wilkinson, J. F., ibid., 1949, **1**, 11.
[3] Baird, I. M., and Podmore, D. A., ibid., 1954, **2**, 942.
[4] Basu, S. K., ibid., 1963, **1**, 1430.
[5] Marchasin, S., and Wallerstein, R. O., *Blood*, 1964, **23**, 354.
[6] Clay, B., Rosenberg, B., Sampson, N., and Samuels, S. I., *Brit. med. J.*, 1965, **1**, 29.
[7] Ibid., 1963, **2**, 367.
[8] O'Sullivan, D. J., Higgins, P. G., and Wilkinson, J. F., *Lancet*, 1955, **2**, 482.
[9] Israëls, M. C. G., and Cook, T. A., ibid., 1965, **2**, 654.

Deficiency of Fibrin-stabilizing Factor

In 1944 K. C. Robbins[1] observed that fibrin produced by adding separated thrombin to fibrinogen differed in solubility from fibrin formed when plasma was allowed to clot. Subsequently K. Laki and L. Lóránd[2] found that clots from plasma were insoluble in 30% urea solution, whereas fibrin formed from purified fibrinogen was soluble. The "plasma fibrin" was different from "pure fibrin" not only in solubility but also in its mechanical strength and when studied by *x*-ray diffraction. The substance present in plasma or serum which alters the structure of the fibrin was called fibrin-stabilizing factor, or more recently Factor XIII.

For many years Factor XIII remained an interesting academic entity with no special significance for the clinical pathologist. In 1960, however, F. Duckert and his colleagues[3]

[1] Robbins, K. C., *Amer. J. Physiol.*, 1944, **142**, 581.
[2] Laki, K., and Lóránd, L., *Science*, 1948, **108**, 280.
[3] Duckert, F., Jung, E., and Shmerling, D. H., *Thrombos. Diasthes. Haemorrh.(Stuttg.)*, 1960, **5**, 179.
[4] Barry, A., and Delâge, J. M., *New Engl. J. Med.*, 1965, **272**, 943.
[5] *Brit. med. J.*, 1965, **1**, 1122.