assay of the urinary excretion of oestrone. Women who excrete more than 5 μg. of oestrone per 24 hours have evidence of some residual ovarian activity and are likely to respond to the drug. A nonspecific method for assaying oestrogen, such as that successfully employed by Dr. D. Ferriman and his colleagues (page 444), gives some indication of ovarian response, but its sensitivity in distinguishing between those patients who are likely to respond to clomiphene and those who are not may be questioned. They found that patients with menstrual cycles of less than six months were more likely to respond successfully to clomiphene than those with longer cycles.

Women whose endogenous ovarian activity is sufficient for them to have fairly regular menstruation but who do not ovulate are the most rewarding group for clomiphene therapy, but they are also the most difficult to identify with any assurance. Endometrial biopsy and assay of urinary pregnanediol are more reliable means of detecting ovulation than basal temperature charts. Even for a nulliparous woman an endometrial biopsy should not entail more than a few hours in hospital and does not require an anaesthetic. The assay of urinary steroids like pregnanediol and oestrone is a different matter. These procedures have been out of the research stage for more than a decade, but few teaching hospitals have initiated specific techniques for carrying them out, most clinical centres lack facilities for doing them, and some use simplifications which are inadequate for clomiphene therapy.

There is little point in starting clomiphene therapy unless it can be established that the woman does not ovulate, is capable of ovulation, and has a fertile husband. To this end gonadotrophin assays are helpful, but they are available to few patients. Oestrogen and pregnanediol assays are well-nigh essential, and a semen analysis is mandatory. To determine whether a woman responded at all to clomiphene and when she ovulated requires nearly continuous 24-hour collections of urine for steroid assays over two to three weeks. This can be done on an outpatient basis ; the diagnosis and therapy can be undertaken only with the aid of a specialist clinic. Without the collaboration of such services the use of clomiphene in general practice is clearly unwise. It is a fine example of a situation where the skilful use of laboratory resources can be of great benefit to a few people while a failure to use them can do harm to a larger number.

Blue Blood

In these days of egalitarianism blue blood is no longer the much sought after prerequisite of the nobility ; indeed, it has of late become fashionable to disclaim such an inheritance. Nature unfortunately cannot be so denied ; we are all the inheritors of blue blood, or almost all. Those of us who are not so endowed are certainly severely underprivileged members of the community, though it will take more than an Act of Parliament to put things right. Normal plasma contains a blue copper protein, caeruloplasmin, first isolated by C. G. Holmberg and C. B. Laurell[1 2] in 1947 and 1948 and so named because of its colour. In 1952 I. H. Scheinberg and D. Gitlin[3] showed that in patients with Wilson's disease this protein was markedly deficient or even entirely absent from the plasma, and they suggested that this was the primary metabolic defect in the disease.

The Scheinberg hypothesis was entirely reasonable ; failure to elaborate this normal plasma protein resulted in the plasma copper remaining diffusable so that it entered the tissues in abnormal amounts. This led to basal ganglia degeneration in the brain and consequently to the bizarre sequence of motor disturbances which are so characteristic of the disease. In the liver excess copper led to necrosis and fibrosis, in the kidneys to defects of tubular reabsorption, and in the eyes to the typical Kayser-Fleischer pigment rings which are diagnostic of the disease. Unfortunately, as G. E. Cartwright and his associates[4] have pointed out, in their experience—which mirrors that of most workers in this field—there is a poor correlation between caeruloplasmin concentration and the duration and severity of the clinical course of the illness. In fact, patients are occasionally seen with perfectly normal levels of this protein in their blood, as was early reported by A. G. Bearn and H. G. Kunkel[5] and also by Cartwright's group.[6]

One possible explanation of this discrepancy, and a very attractive one at that, was the hypothesis that the caeruloplasmin present in some patients with Wilson's disease was structurally and therefore functionally abnormal. Thus there might be two different alleles mediating the disease, one leading to failure of protein synthesis and one to abnormalities of protein structure, either of which could give rise to the same disastrous functional derangement in the transport of copper in the body. This theory was discussed by a number of delegates at the London meeting on Wilson's disease held at the National Hospital in 1960,[7] but we have had to wait for seven years before further light has been thrown on this aspect of the problem. Now N. A. Holtzman and his colleagues[8] working at the Johns Hopkins Hospital in Baltimore have isolated and crystallized caeruloplasmin from a patient with Wilson's disease in whom the concentration of this protein in the blood approached normal levels. Their findings of a normal tryptic peptide map go a long way to disproving the theory of a structurally abnormal caeruloplasmin in Wilson's disease. These workers note, as others have done, that when treatment with penicillamine is instituted caeruloplasmin disappears from the plasma, and they postulate the occurrence of a reduced rate of synthesis of caeruloplasmin in their patient ; when the excess copper stores were removed by penicillamine the stimulus to further synthesis of the protein became inadequate. This may well be true, but unfortunately it takes us no further in our understanding of the disease. Indeed, one of the main stumbling-blocks to our understanding of the pathogenesis of this mysterious illness is the complete absence of clues to the normal function of caeruloplasmin.[9] L. Broman[10] has even described it as " just an ineffective oxidase, in the wrong place, lacking a suitable substrate," but he himself believes that it represents a transport form of a copper-containing prosthetic

1 Holmberg, C. G., and Laurell, C. B., *Acta chem. scand.*, 1947, **1**, 944.
2 —— —— ibid., 1948, **2**, 550.
3 Scheinberg, I. H., and Gitlin, D., *Science*, 1952, **116**, 484.
4 Cartwright, G. E., Markowitz, H., Shields, G. S., and Wintrobe, M. M., *Amer. J. Med.*, 1960, **28**, 555.
5 Bearn, A. G., and Kunkel, H. G., *J. clin. Invest.*, 1954, **33**, 400.
6 Markowitz, H., Gubler, C. J., Mahoney, J. P., Cartwright, G. E., and Wintrobe, M. M., ibid., 1955, **34**, 1498.
7 *Wilson's Disease : Some Current Concepts*, ed. J. M. Walshe and J. N. Cumings, Oxford, 1961.
8 Holtzman, N. A., Naughton, M. A., Iber, F. L., and Gaumnitz, B. M., *J. clin. Invest.*, 1967, **46**, 993.
9 Holmberg, C. G., in *Wilson's Disease : Some Current Concepts*, ed. J. M. Walshe and J. N. Cumings, Oxford, 1961, p. 64.
10 Broman, L., *Acta Soc. Med. upsalien*, 1964, **69**, suppl. No. 7.
11 Osborn, S. B., and Walshe, J. M., *Lancet*, 1967, **1**, 346.
12 Aisen, P., Morell, A. G., Alpert, S., and Sternlieb, I., *Nature*, 1964, **203**, 873.

group which acts as an oxygen-activating unit in cytochrome oxidase. Unfortunately this theory too falls foul of the facts, which have an unpleasant habit of invalidating all the theories about this disease as fast as they are put forward. As S. B. Osborn and J. M. Walshe[11] pointed out earlier this year, it is possible for a patient with Wilson's disease, treated with pencillamine, to live a perfectly normal life with no symptoms of disease and with no detectable copper or caeruloplasmin in his serum—always provided that the drug is continued and the patient maintained in copper balance. So this would suggest an excretory function for caeruloplasmin. But this theory comes up against the work of the Albert Einstein group of workers,[12] who have shown, at least for rabbits, that the copper of catabolized caeruloplasmin "is not directly or preferentially excreted by hepatic, pancreatic, intestinal, or renal routes." Blue blood may be all very well in preventing Wilson's disease, but the way in which it mediates this function is as obscure as its role in ennobling the nobility.

Obstructive Airways Disease

The clinical features of the bronchial and emphysematous types of obstructive airways disease have been defined by A. C. Dornhorst[1] and T. Simpson[2] and their physiological characteristics by C. Ogilvie[3] and by W. A. Briscoe and A. Cournand.[4] The careful and detailed studies of C. M. Fletcher, B. Burrows, and others[5 6] firmly established the criteria whereby these two types can be distinguished. These workers have also tackled the semantic problem posed by the indiscriminate use of the terms "chronic bronchitis" and "emphysema," the first being favoured in Britain and the second in America. Using standardized clinical, radiographic, and physiological techniques, they compared 50 patients from a "bronchitis" clinic in London with 50 patients attending an "emphysema" clinic in Chicago.[7] Apart from a rather greater incidence of disabling chest illness in London, there was no real difference in the pattern of obstructive airways disease for the two cities. In particular, the frequency of the bronchial and emphysematous forms was the same.

N. L. Jones, Burrows, and Fletcher[8] have now extended this study by carrying out an annual review of the original 100 patients over a period of three years. During this time progress and mortality were remarkably similar in the two cities, but the incidence of disabling chest illness was higher among the London patients. However, a detailed questionary showed that bronchitic exacerbations were not in fact more frequent in London than in Chicago but only more disabling in terms of the time spent in bed or off work. The authors attribute this to differences in working conditions, sickness benefits, and cost of treatment between the two cities rather than to differences in the behaviour of the disease process itself.

This recent survey also gives valuable information on the relative prognosis of the two types of obstructive airways disease. The mortality was higher in the bronchial (36%) than in the emphysematous group (15%), and this was related to the greater incidence of hypercapnia among the bronchitic patients. It might have been thought that the complications of bronchitis (infection, hypercapnia, and right heart failure) would prove more amenable to treatment than the irreversible lung changes of emphysema. The actual finding of a much higher death rate for bronchitis surely points to the need for a reappraisal of therapeutic methods used in this formidable disease. The thorough techniques of investigation evolved by Fletcher and his co-workers could well provide the basis for a study of this kind.

[1] Dornhorst, A. C., *Lancet*, 1955, **1**, 1185.
[2] Simpson, T., *Tubercle (Lond.)*, 1958, **39**, 307.
[3] Ogilvie, C., *Thorax*, 1959, **14**, 113.
[4] Briscoe, W. A., and Cournand, A., *Ciba Foundation Symposium on Pulmonary Structure and Function*, ed. A. V. S. de Reuck and M. O'Connor, 1962, p. 304. Boston.
[5] Fletcher, C. M. Hugh-Jones, P., McNicol, M. W., and Pride, N. B., *Quart. J. Med.*, 1963, **32**, 33.
[6] Burrows, B., Fletcher, C. M., Heard, B. E., Jones, N. L., and Wootliff, J. S., *Lancet*, 1966, **1**, 830.
[7] Fletcher, C. M., Jones N. L., Burrows, B., and Niden, A. H., *Amer. Rev. resp. Dis.*, 1964, **90**, 1.
[8] Jones, N. L., Burrows, B., and Fletcher, C. M., *Thorax*, 1967, **22**, 327.

Realism and Addicts

The Ministry of Health is facing increasing criticism because of its alleged dilatoriness in responding effectively to the threat of epidemic heroin addiction in Britain. A brief inquiry published by the *Guardian*[1] last week certainly gives a picture more of disarray than preparedness so far as hospital services are concerned, while a speaker at a recent meeting of the General Medical Services Committee[2] denounced "a typical Ministry paper scheme," which he alleged was simply putting forward proposals which could not be implemented owing to lack of facilities. To what extent are such strictures justified?

The latest "paper scheme" is a memorandum dealing with the rehabilitation and aftercare of heroin addicts.[3] The G.M.S. Committee has already drawn attention to the inappropriateness of the use of the allocation procedure to place an addict on a general practitioner's list, but otherwise the ideas put forward in this memorandum deserve nothing but praise. It presents a humane and intelligent approach to the problem of drug addiction, stressing that detoxification by itself is not enough, and picturing narcotic addiction as requiring comprehensive integrated services—clinics, hospitals, hostels, work-training—rather than mere drug-handout centres. The memorandum supplements the model for hospital treatment which was put forward earlier this year.[4]

The trouble comes when turning from the Ministry's memoranda to the realities. Those in Alexander Fleming House seem to have some of the characteristics of the kind of student who writes alpha papers but muffs the practicals. To take an example: one of the most important proposals in the new circular concerns the role of hostels in the aftercare of addicts, and the benefits that can result from grouping patients are discussed with a degree of sympathy and insight which is admirable: "Although the establishment of a disciplined atmosphere is essential this alone is insufficient to prevent drug taking. It is necessary to build up an atmosphere of co-operation between staff and residents and in this task the psychiatrist can give valuable assistance. . . . The expectation of the hostel must not be set too high and staff must accept the probability that relapse will take place and be ready to contend with its effects on other residents and themselves." A splendid answer in a written paper, but then take the example further and look at the performance in the practicals.

[1] *The Guardian*, 16 November 1967.
[2] *Brit. med. J. Suppl.*, 1967, **4**, 47.
[3] *Ministry of Health Memorandum*, H.M. (67) 83.
[4] Ibid., H.M. (67) 16.
[5] *Brit. med. J.*, 1967, **3**, 692.
[6] Ibid., 1967, **4**, 366.