(11 November, p. 366) but in my case I have been on the receiving end of the patients. When a new syndrome is recognized it is not enough to report its existence; one should also try to establish its cause.

The cases I have seen occurred for two reasons. The majority were due to the original doctor failing to explain adequately (or even at all) the nature and effects of the patient's illness or, more usually, the nature of and reasons for investigations and treatment. A small number were due to inadequate investigations or therapy. The supercilious term "middle class syndrome" glosses over these underlying causes; the cases arise because the patients happen to be intelligent and articulate, and by accident have unorthodox access to a member of the medical profession. It would be more honest (an attribute we often lack when examining ourselves and our shortcomings) to call this syndrome the "dissatisfied patient syndrome."

I agree with Dr. Morgan's implied deprecation of any new investigations and treatment in this sort of situation not being discussed with the family doctor (although it is ironical that the main cause of the syndrome is failure of communication). However, I cannot agree that these cases will be eliminated by doctors maintaining their ethical code in their relations with one another. The syndrome will disappear (except for the very few patients who actually enjoy multiple consultations) by application of our primary ethic—our responsibility to the patient.—I am, etc.,

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Detecting Sickle Haemoglobin

SIR,—I fully support Professor J. E. Bowman (9 September, p. 644) in advocating definitive electrophoresis and identification of sickle haemoglobin rather than short-cut visual or automated[1] screening methods, a modification (I doubt for the better) of the solubility test.[2] The use of whole blood in solubility testing[1] may lead to false positives in cases of leukemia, high plasma proteins, etc.

Where there is a high incidence of sickle haemoglobin, as in Negroes, Asians, and Mediterranean peoples, other haemoglobin variants—e.g., C, D, E, G, J, thalassaemia, etc.—occur. Both electrophoretic *and* solubility tests are essential for the correct identification of these and haemoglobins SS, AS, SC, S/thalassaemia, S/high F, etc. There are 34 haemoglobin variants with electrophoretic mobility identical or similar to that of sickle haemoglobin; half these have abnormalities (unstable haemoglobins or haemoglobins with abnormal oxygen affinities) in the heterozygous form and are clearly distinguishable from haemoglobin AS by routine haematological tests, including those for heat stability and Heinz bodies. With a bank of six micro-electrophoresis chambers and double spot application[3] 384 samples can be processed per technician-day.[4] Apart from screening out haemoglobins with electrophoretic mobilities different from that of sickle haemoglobin, one is alerted to α- and β-thalassaemia. Undetected benign sickle-cell anaemia[5] is also immediately apparent.

Apart from sickle haemoglobin, haemoglobins C Harlem (C Georgetown identical), Memphis/S, Barts and H (α-thalassaemia), and I have reduced solubilities when deoxygenated. Using automatic pipettors, 480 visual dithionite (and urea-dithionite) tests can be completed daily at a fraction of the cost of automated methods.[1 6] Further, automatic analysers would have quantitative assays as priority in most parts of the world where sickle haemoglobin is prevalent.

Electrophoresis and solubility testing done pari passu thus delineate the major haemoglobinopathies, sickle haemoglobin and double heterozygotes with other variants, and α- and β-thalassaemias. These are mainly associated with similar ethnic groups and geographical localities.[7] In Indians, Iranians, Negroes, etc. haemoglobin D, a non-sickler with electrophoretic mobility identical to that of sickle haemoglobin, requires to be clearly distinguished. With a heat stability test for unstable haemoglobins, these tests would screen all major haemoglobin variants with serious social and clinical effects.

Nalbandian's programme[8] screens all new pupils entering the school system. The social and psychological trauma at this stage is considerable; it would be far better to perform the screening towards the end of the schooling period or on school-leaving, as advocated for β-thalassaemia screening in London Cypriots.[9] The sickle-trait bearer is not at risk except under conditions of stress; only on marriage between partners with the sickle or thalassaemia trait have the offspring a one-in-four chance of suffering from sickle-cell anaemia or thalassaemia major.

With the rising tide of Asian, West Indian, and Mediterranean immigration into the United Kingdom over the past decade a problem of some magnitude in sickle haemoglobin and thalassaemia is developing. Clearly, screening programmes will avert risks by the use of genetic information and alert patients and clinicians to the medical requirements of patients with sickleaemia.—I am, etc.,

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1 Nalbandian, R. M., *et al.*, *Clinical Chemistry*, 1971, **17**, 1033.
2 Itano, H. A., *Archives of Biochemistry and Biophysics*, 1953, **47**, 148.
3 Fingerhut, B., and Ortez, A., *Clinical Chemistry*, 1971, **17**, 34.
4 Bernstein, R. E., *South African Medical Journal*, 1969, **43**, 1455.
5 Sergeant, G. R. Richards, R., Barbor, P. R. H., and Milner, P. F., *British Medical Journal*, 1968, **3**, 86.
6 Nalbandian, R. M., Nichols, B. M., Heustis, A. E., Prothro, W. B., and Ludwig, F. E., *Journal of the American Medical Association*, 1971, **218**, 1680.
7 Livingstone, F. B., Abnormal Hemoglobins in *Human Populations*, Chicago, Aldine Publishing Co., 1967.
8 Nalbandian, R. M., *Journal of the American Medical Association*, 1972, **221**, 500.
9 Modell, C. B., Benson, A., and Wright, C. R. P., *British Medical Journal*, 1972, **3**, 737.

Gentamicin Dosage

SIR,—Dr. J. H. Darrell (18 November, p. 427) is quite correct in drawing attention to the confusion which reigns over the dose schedule for gentamicin. This antibiotic is one of the most powerful available to the clinician, but there is a tendency to be too cautious in its use, resulting in underdosage. The use of larger doses at eight-hourly intervals which Dr. Darrell advocates would certainly produce bactericidal levels even against *Pseudomonas* species. A further problem arises in a patient with normal renal function, in that the serum levels will be below the desirable therapeutic level for a considerable part of the eight hours.

The application of pharmacokinetic principles to the problem may well be useful. The two variables which the clinician can alter are the dose (D) and the dosing interval (T). Accepting the limitations of a one-compartment model these can be calculated using the formula

$$C_\infty = \frac{F.\,D}{V_d.\,K_e.\,T}$$

where C_∞ is the mean serum level after multiple dosing, V_d the distribution volume, F the fraction of the dose absorbed (= 1 in this case), and K_e the elimination constant for gentamicin. This gives dosing schedules of (*a*) 40 mg intramuscularly 2-hourly, (*b*) 80 mg intramuscularly 4-hourly, or (*c*) 120 mg intramuscularly 8-hourly to achieve a mean serum level of 5 μg/ml.

The elimination constant (K_e) is derived[1] from a knowlegde of the half-life[2] ($t_{\frac{1}{2}}$) of gentamicin:

$$K_e = \log_e 2 \times \frac{1}{t_{\frac{1}{2}}}$$

The volume of distribution for gentamicin[2] is variable but a mean value is 15 l.

Obviously the use of smaller doses more frequently will give rise to less fluctuation in the serum level and avoid the possibility of the peak level coming into the toxic range. In renal failure the serum half-life will lengthen, and to achieve the same mean serum level the dosing interval should be lengthened.—We are, etc.,

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1 Janku, I., in *Fundamentals of Biochemical Pharmacology*, ed. Z. M. Bacq. Oxford, Pergamon, 1971.
2 Gyselynck, A-M., Forrey, A., and Cutler, R., *Journal of Infectious Diseases*, 1972, **124**, S.70.

SIR,—The letter by Dr. J. H. Darrell (18 November, p. 427) emphasizing the need for adequate dosage with gentamicin is timely. We would, however, extend this observation to include paediatric practice. We have recently carried out serum assays, using the vertical diffusion technique,[1] on two children aged 5 months and 4 years, both of whom received the standard recommended dose of 0·8 mg/kg body weight three times a day by intramuscular injection. Gentamicin levels at one hour were 3·3 μg/ml and 1 μg/ml respectively. The latter level in particular must be regarded as subtherapeutic.

Evidence has been produced by a number of workers[2-4] that larger doses than those routinely recommended by the manufacturers must be given to neonates and young children if therapeutic levels are to be achieved. For instance, a figure of 2·5 mg/kg 8- or 12-hourly in neonates reducing to adult dosage in older children has been suggested. We understand that evidence is to be submitted to the Medicines Commission by the manufacturers in order to obtain permission to use new dosage recommendations in children. In the meantime we would strongly recommend that the use of gentamicin in children and neonates be