et al. (1965) that the smokers have both higher values in the younger age groups and a steeper decline with age than the non-smokers.

The constant term of the regression is more variable between the different series than the coefficients on height and age. Part of this is technical—for example, Ferris *et al.* find an average difference of 0.164 l. between the maximum F.E.V. and the mean of the last three out of a total of five determinations. The use of equipment having different flow characteristics, and calibration errors, may also have contributed to the systematic differences observed. Part is due to environmental factors—for example, smokers often achieve an increase in F.E.V. when they give up smoking, and a reduction in atmospheric pollution may be expected to have a similar beneficial effect (cf. Holland and Reid, 1965).

The role of constitutional factors in determining the F.E.V. may be defined with greater certainty when more data are available for rigorous statistical analysis. This may come through the International Biological Programme and the activities of the International Labour Office and World Health Organization. Knowledge of the effect of environmental factors will similarly come from the many epidemiological surveys now in progress. Meanwhile on account of its broad basis the present relationship may be of use to those wishing to compare their average results with those of others. For example, it is of interest to us that the mean value for the F.E.V.₁ in men aged 55–64 years on the island of Bornholm (Olsen and Gilson, 1960) is in exact agreement with the present finding.

The prediction of expected values for individuals, on account of variability between subjects, is less exact than for groups; it is best done by reference to the measured values for a representative sample drawn from the community in question. Where such data are not available the present relationship may be substituted, either as it stands or, if there are data available for one age-and-height group, after adjustment to the constant term. For example, in the case of Bornholm the only available data are for the 55–64 age group, and these are in close agreement with the overall relationship: the latter is therefore the best available estimate for the other age groups. If the average value in the selected group had been *x* ml. below predicted, then for application to the population this amount should be subtracted from that given by the relationship. However, the extent to which it is justifiable to extrapolate in this way will vary from one community to another, and should be submitted to practical confirmation at the first opportunity. Without more evidence extrapolation is not justifiable for other ethnic groups in whom lower values for the F.E.V. have been reported: these

include the inhabitants of the subcontinent of India (Rao *et al.*, 1961; Cotes and Malhotra, 1965), the Maori of New Zealand (Glass, 1962), and members of some African races (Paul *et al.*, 1960; Gilson *et al.*, 1962). These racial differences have still to be explored.

Summary

A linear regression of forced expiratory volume (F.E.V.₁) on age and height is reported for 275 healthy male subjects living in the United Kingdom. The regression coefficients are similar to those reported from other countries in N.W. Europe and N. America. The equations have therefore been combined to yield the following overall relationship, which may be of use for predicting average normal values:

$$\text{F.E.V.}_1 = 3.62 \text{ Ht (m.)} - 0.031 \text{ age (years)} - 1.41 \text{ (S.D. } > 0.5) \text{ l B.T.P.S.}$$

The limitations to the use of this relationship are discussed.

We are indebted to Miss A. Hart, Mrs. C. John, and Miss C. Wilton for technical assistance.

REFERENCES

- Berglund, E., Birath, G., Bjure, J., Grimby, G., Kjellmer, I., Sandqvist, L., and Söderholm, B. (1963). *Acta med. scand.*, **173**, 185.
 Cara, M., Sadoul, P., and Bolt, W. (1961). *C.R. Soc. Biol. (Paris)*, **155**, 52.
 Cotes, J. E., and Malhotra, M. S. (1965). *J. Physiol. (Lond.)*, **177**, 17–18P.
 de Kroon, J. P. M., Joosting, P. E., and Visser, B. F. (1964). *Arch. Mal. prof.*, **25**, 17.
 Doll, R., and Hill, A. B. (1950). *Brit. med. J.*, **2**, 739.
 Ferris, B. G., Anderson, D. O., and Zickmantel, R. (1965). *Amer. Rev. resp. Dis.*, **91**, 252.
 Gilson, J. C., Stott, H., Hopwood, B. E. C., Roach, S. A., McKerrow, C. B., and Schilling, R. S. F. (1962). *Brit. J. industr. Med.*, **19**, 9.
 Glass, W. I. (1962). *N.Z. med. J.*, **61**, 433.
 Higgins, I. T. T. (1957). *Brit. med. J.*, **2**, 1198.
 — (1959). *Ibid.*, **1**, 325.
 — and Cochran, J. B. (1958). *Tubercle (Lond.)*, **39**, 296.
 — Cochran, A. L., Gilson, J. C., and Wood, C. H. (1959). *Brit. J. industr. Med.*, **16**, 255.
 — and Oldham, P. D. (1962). *Ibid.*, **19**, 65.
 — Cochran, A. L., and Gilson, J. C. (1956). *Brit. med. J.*, **2**, 904.
 Holland, W. W., and Reid, D. D. (1965). *Lancet*, **1**, 445.
 Jouasset, D. (1960). *Poumon*, **16**, 1145.
 Kory, R. C., Callahan, R., Boren, H. G., and Syner, J. C. (1961). *Amer. J. Med.*, **30**, 243.
 McKerrow, C. B., McDermott, M., and Gilson, J. C. (1960). *Lancet*, **1**, 149.
 Medical Research Council (1960). *Brit. med. J.*, **2**, 1665.
 Olsen, H. C., and Gilson, J. C. (1960). *Ibid.*, **1**, 450.
 Paul, R., Fletcher, G. H., and Addison, G. (1960). *Med. Proc.*, **6**, 69.
 Rao, M. N., Sen, G. A., Saha, P. N., and Devi, A. S. (1961). *Indian Coun. med. Res. spec. Rep. Ser.*, No. 38.
 Wilson, R. H., Meador, R. S., Jay, B. E., and Higgins, E. (1960). *New Engl. J. Med.*, **262**, 956.

Further Case of Histidinaemia

GILLIAN A. CLARANCE,* M.B., D.OBST.R.C.O.G., D.C.H.; J. K. BOWMAN,† B.Sc.

Brit. med. J., 1966, **1**, 1019–1020

Increasing attention is being focused on the “false-positive” Phenistix test (Hudson *et al.*, 1963; Coffey, 1964). The following case of histidinaemia was detected as a result of this. Ghadimi *et al.* (1962) first described a case of histidinaemia and demonstrated an excess of histidine in plasma and urine. Subsequently Auerbach *et al.* (1962) showed the defect to be due to a deficiency of the enzyme histidase (Fig. 1), and agreed with Ghadimi *et al.* that the positive reaction with ferric chloride

resulted from the presence of imidazole pyruvic acid in the urine.

That there are no consistent clinical findings in this disorder is agreed. Initially, cases were reported of patients who were mentally normal but had a speech defect (Auerbach *et al.*, 1962; La Du *et al.*, 1963a, 1963b; Woolf, 1965). Subsequently the cases of severely physically and mentally handicapped patients who suffered from intercurrent infections and convulsions were reported (Davies and Robinson, 1963; Holton *et al.*, 1964). The present report concerns an older child who was

* Paediatric Registrar, Plymouth General Hospital.

† Biochemist, Plymouth General Hospital.

physically and mentally retarded, but not to the degree described in the latter case reports.

Case Report

A 13-year-old illegitimate girl was admitted to hospital from a home for retarded children because of a recurrence of encopresis. She had resided at this home since the age of 5 years, when her I.Q. was 68 (revised Stanford-Binet); at 6 years her I.Q. was 72. She is said to have walked at 2 years, and to have spoken single words at 4. There was no history of an abnormal number of inter-current infections or of convulsions.

On admission to hospital she was noted to have a "short, squat" appearance, blue eyes, and light-brown hair. Her height was 52 in. (132 cm.) and her weight 72 lb. (32.6 kg.), the former being considerably below the third percentile and the latter just below it. Her speech was immature and her I.Q. was assessed as 54 (Terman-Merrill).

A search for the possible cause of her physical and mental retardation revealed, in the urine, a "positive" Phenistix test (greyish green) and a slowly developing dark-green colour with ferric chloride.

Investigations

Two-way amino-acid paper chromatography of the urine and serum was performed. The chromatograms were run in two different solvent systems: (1) butanol/acetic acid/water followed by butanol/pyridine/water, and (2) butanol/acetic acid/water followed by phenol/ammonia. This was done on several occasions over a period of weeks, with similar results on each occasion. The amounts were quantitated on the Technicon amino-acid AutoAnalyzer at Alder Hey Hospital, a single specimen of blood and a sample from a 24-hour collection of urine being used for this purpose. The

FIG. 2.—Chromatogram showing imidazoles (Pauly).

serum histidine level was 11.2 mg./100 ml. and that in the urine 599 mg./24 hours; the histidine clearance was 4.19 ml./min./1.73 sq.m. (normal values 4.0–9.7), showing that this is an overflow, not a renal amino-aciduria.

The Pauly stained urine chromatogram (Fig. 2) showed, in addition to histidine, the presence of considerable amounts of imidazole pyruvic acid and imidazole acetic acid, but these were not detected in the serum.

A skin histidase assay was made on single specimens on two separate days according to the technique of Zannoni and La Du (1963) with homogenates of stratum corneum, samples being obtained from heel scrapings. A composite sample of stratum corneum from four adults was used for a control assay, and the result of 4.3 μmols urocanic acid/hr./g. tissue fell within the accepted normal adult range. The assay is based on the accumulation of urocanic acid; the results are given in Table I. The readings were made on the two-hour tube against a zero time-tube. It would appear from these figures, no urocanic acid being formed, that there is no histidase activity in the patient's skin.

TABLE I.—Skin Histidase Assay

	Control Adult	Patient Day 1	Patient Day 2
μmols Urocanic acid/hr./g.	4.3	Nil	Nil

Accepted normal range: adult, 1.8–5.3 μmols urocanic acid/hr./g.; child, 4.2–6.6.

A histidine loading test gave the results shown in Table II. Day 1 is the base line, and Day 2 after a loading dose of histidine monohydrochloride 0.1 g./kg. body weight. Other amino-acids were present, but the amounts were relatively insignificant.

TABLE II.—Histidine Loading Test

	Day 1 610 ml.	Day 2 710 ml.
Total volume of urine/24 hr.	610 ml.	710 ml.
Amino-acid:		
Threonine	150.3	161.6 mg./day
Serine	127.5	24.6 "
Glutamic acid	4.8	29.2 "
Glycine	143.5	157.1 "
Alanine	40.8	55.6 "
Lysine (includes methyl histidine)	19.3	11.3 "
Histidine	372.0	648 "

Summary and Conclusions

A further case of histidinaemia with mental and physical retardation was found as a result of a "false-positive" Phenistix test.

To date, the patient, aged 13, is the oldest child reported to have had this disorder, and it is interesting that the clinical findings seem to represent the middle of the "spectrum" of cases so far described.

Dietary treatment at this age is unlikely to be beneficial and a trial is unjustified. It has not been possible to investigate any of the family.

We wish to thank Dr. J. N. Montgomery, under whose care the patient was admitted, for his help and encouragement, and for allowing us to publish this case. Also our thanks are expressed to Dr. G. A. C. Lynch, in whose department the biochemical investigations took place, and Mr. J. T. Ireland, of Alder Hey Children's Hospital, Liverpool, for quantitating the amino-acids and giving valuable advice.

REFERENCES

Auerbach, V. H., DiGeorge, A. M., Baldrige, R. C., Tourtellotte, C. D., and Brigham, M. P. (1962). *J. Paediat.*, **60**, 487.
Coffey, V. P. (1964). *J. Irish med. Ass.*, **54**, 84.
Davies, H. E., and Robinson, M. J. (1963). *Arch. Dis. Childh.*, **38**, 80.
Ghadimi, H., Partington, M. W., and Hunter, A. (1962). *Pediatrics*, **29**, 714.
Holton, J. B., Lewis, F. J. W., and Moore, G. R. (1964). *J. clin. Path.*, **17**, 671.
Hudson, F. P., Dickinson, R. A., and Ireland, J. T. (1963). *Pediatrics*, **31**, 47.
La Du, B. N., Howell, R. R., Michael, P. J., and Sober, E. K. (1963a). *Ibid.*, **31**, 39.
— Howell, R. R., Jacoby, G. A., Seegmiller, J. E., Sober, E. K., Zannoni, V. G., Canby, J. P., and Ziegler, L. K. (1963b) *Ibid.*, **32**, 216.
Woolf, L. I. (1965). *Proc. Ass. clin. Biochemists*, **3**, 176.
Zannoni, V. G., and La Du, B. N. (1963). *Biochem. J.*, **88**, 160.