In this trial the point is demonstrated by the fact that improvement was recorded by general practitioners in approximately 75% of patients who completed the course, while only two patients (one on active and one on inert tablets) were reported to be worse. This is underlined when one compares the opinion of the general practitioners with those of the members of the panel. However, it must be remembered that in a condition such as acne vulgaris one has to consider the remissions and exacerbations which occur as part of the disease and which are associated with such factors as sunlight and menstruation. Straumfjord (1943) listed others, such as heredity, puberty, endocrine upset, seborrhoea, diet, digestive upset, infection, disturbance in water balance, and psychoneurosis. The small numbers in this trial did not permit analysis of these factors.

In the present trial there was no evidence that vitamin A had caused improvement or increased the chance of remissions that normally occur in acne from time to time, and without a double-blind trial such as this the normal fluctuations might have led to an over-optimistic opinion of benefit. In contrast, however, results did suggest that deterioration was lessened by the use of this treatment. Out of 13 people whose skin conditions were deemed to be worse at the end of the trial only two were on active tablets. This group is very small and the difference is significant only at the 2% level ($\chi^2=5.9$). Furthermore, recorded results in each case were based on a majority opinion of the panel of three. It follows that it would be prudent to follow up this observation with a further trial before coming to a final conclusion.

In assessing these results one should remember that some workers, such as Coombes, Saperstein, and Distelheim (1949), believe that vitamin A has to be given for at least three months before beneficial effects are noted. It may be argued that the duration of the present trial was too short, but it was felt that the onset of sunnier weather might influence the course of the disease. This climatic factor is rarely stressed in the literature on this subject.

The observation that improvement occurred equally with inert and active tablets is fairly conclusive from both the clinical and the photographic evidence. We suggest, however, that photography is more acceptable as an objective method of evaluating results than clinical impressions provided that the same routine is followed carefully on each occasion. Once room-lighting, colour background, and exposure are carefully standardized, the actual photographing is brief and easy to effect. Furthermore, it would be possible to resubmit the transparencies to the same or another panel to confirm the results.

Summary

A double-blind trial of oral vitamin A in the treatment of acne vulgaris is described, 150,000 I.U. being given daily for 12 weeks.

Colour transparencies of the left side of the face were taken before and after treatment under standard conditions, and these were used as an objective method of assessing results of treatment by a panel of three. ♦

There is no evidence that vitamin A is more likely to cause improvement than inert tablets.

The dangers of relying upon clinical impressions of doctor and patient to judge the value of a remedy used in a therapeutic trial are demonstrated.

The relative merits of photography and clinical impression as indices of improvement in acne vulgaris are discussed.

The Faculty would like to acknowledge with thanks the advice and help given by Dr. Grant Peterkin, consultant dermatologist to the Royal Infirmary, Edinburgh. The Faculty is also grateful to Mr. S. A. Sklaroff for statistical advice and to Dr. M. Briggs, of Roche Products Limited, who kindly provided the active and inert tablets and donated the photographic equipment.

The following members and associates of the Faculty took part in the therapeutic trial: J. A. D. Anderson, J. T. Baldwin, E. S. Blackadder, J. D. Cruickshank, W. S. Dalgetty, W. A. Elliot, S. L. Forrest, T. Hannah, G. Irvine, E. V. Kuenssberg, L. Lamont, A. N. D. Large, A. R. Laurence, J. Lipetz, A. C. McLaren, G. McNaughton, W. W. W. McNeish, J. L. Martin, H. B. Muir, M. E. Munro, J. M. Ross, R. E. Stewart, I. H. Stokoe, W. P. Thomson.

REFERENCES

- Coombes, F. C., Saperstein, R. B., and Distelheim, I. (1949). *Med. Tms (N.Y.)*, **77**, 473.
 Fell, H. B., and Mellanby, E. (1953). *J. Physiol. (Lond.)*, **119**, 470.
 Germeraad, W. F., Vashinder, H., Verbeek, A. M. T. A., and Van Der Sijde, H. R. (1955). *Ned. T. Geneesk.*, **99**, 2358.
 Logan, W. P. D. (1960). *Studies on Medical and Population Subjects No. 14*, vol. II. H.M.S.O., London.
 Lynch, F. W., and Cook, C. D. (1947). *Arch. Derm. Syph. (Chic.)*, **55**, 355.
 Mitchell, G. H., and Butterworth, T. (1951). *Ibid.*, **64**, 428.
 Straumfjord, J. V. (1943). *Northw. Med. (Seattle)*, **42**, 219.
 Unna, P. G. (1894). In J. Orth's *Lehrbuch der speciellen pathologischen Anatomie*, section 8, part 2, p. 348. Hirschwald, Berlin.

Medical Memoranda

Alkaptonuria, Ochronosis, and Arthritis in a Cypriot Woman

Few accounts of patients with multiple complications of ochronosis exist in the English literature. La Du (1960), in his monograph on this condition, makes a plea for more clinical reports on new cases. This paper describes a further case.

CASE REPORT

The patient was a Greek-Cypriot peasant woman who was unsure of her age but was probably 65 to 70 years old. She came from a small isolated village in Cyprus, and had suffered from pain and stiffness in her knees for 20 years and in her back for five years. This had caused her to stoop, and she had taken to using a pair of walking-sticks. She denied any relevant conditions or consanguinity in her family history.

She was dark-skinned, with a severe kyphosis; her height was 55½ in. (1.4 m.). Joint movement was extremely limited at the shoulders and moderately so at the hips and knees. Mobility of the thoracic and lumbar spine was considerably reduced.

Bluish-black pigmentation was seen, through the skin, in the ear cartilages, nasal cartilage, and the extensor tendons of the fingers. There was hyperkeratosis (ascribed to the use of walking-sticks) of the adjacent surfaces of the thumbs and index fingers, and this was similarly pigmented. In each sclera there was a brown triangular area to each side of the cornea (Fig. 1). Black staining of her clothing was found in the areas which had been in contact with axillary sweat.

Pulse and heart sounds were normal, and there was no evidence of cardiac enlargement. B.P. 160/90. A loud aortic midsystolic murmur was probably due to aortic-valve calcification.

Radiology.—Heavy calcification was present in most of the intervertebral disks, with marked narrowing in some disk spaces

(Fig. 2). There was much marginal lipping, but no continuous ossification of the common ligaments. The shoulder- and hip-joints showed severe destructive changes involving the articular cartilage and subarticular bone; and considerable degenerative change had occurred in the knee-joints. There was extensive calcification in the aortic arch, and the heart was normal in size. Intravenous pyelograms and plain films indicated bilateral radio-opaque renal calculi and a double

FIG. 1.—Scleral pigmentation.

pelvis and ureter on each side. The right kidney excreted poorly, and there were some opacities, probably calculi, at the lower end of a dilated ureter.

Pathological Investigations.—The urine contained a trace of albumin, and reduced Benedict's reagent, but a glucose-oxidase test ("clinistix") was negative. When made alkaline the urine

FIG. 2.—Lateral view of thoracic spine, showing calcification of intervertebral disks.

turned dark brown, beginning at the surface, after about 20 minutes. Fresh urine gave a transient blue coloration with ferric chloride. Blood urea, 60 mg./100 ml. Urine concentrated to S.G. 1020; it contained pus cells, and *Escherichia coli* was cultured. Serum electrolytes and proteins, and glucose tolerance curve, were all normal.

Biochemical Studies.—On a daily protein intake of 66.3 g. the mean urinary excretion of homogentisic acid over four days was 4.1 g./day by the iodometric method (Neuberger, 1947). Urinary ammonium nitrogen/total nitrogen ratio averaged 13.9 (normal 2.5–4.5). The blood homogentisic acid level was 1.5 mg./100 ml.

COMMENT

At least 200 cases of alkaptonuria have been recorded (La Du, 1960). Ochronosis usually develops some time after the third decade. This inborn error of metabolism (Garrod, 1908) is due to lack of the enzyme homogentisic acid oxidase (La Du *et al.*, 1958). This leads to accumulation of homogentisic acid, derived by catabolism of phenylalanine and tyrosine. Homogentisic acid in collagen tissue and cartilage forms the pigment of ochronosis, by autoxidation to a polymer (Milch *et al.*, 1957).

Hereditary transmission of the enzyme defect is by a recessive gene, and consanguinity can often be traced. This is more likely to occur in isolated communities, such as that from which our patient had come.

The pigmentation observed in the sclera, superficial cartilage, and tendons is the most constant clinical feature of ochronosis. Whereas the latter pigmentation is seen through the skin, the epidermis of this patient was itself pigmented in the areas of hyperkeratosis. This may have been caused by sweat-staining.

The skeletal complications provide a diagnostic radiological appearance in the spine, and may result in a crippling degree of osteoarthritis. The calcification is associated with pigment deposition in cartilage. A similar process within collagen tissue leads to calcification in the endocardium and aortic intima (Lichtenstein and Kaplan, 1954) and the genito-urinary tract (Young, 1944).

Most forms of dietary animal protein contain approximately 4% phenylalanine and 4% tyrosine (Block and Bolling, 1951), about 85% of which is catabolized via homogentisic acid. The 66.3 g. protein intake would therefore have supplied 5.3 g. of these amino-acids, which would be expected to yield 4.5 g. of homogentisic acid in the urine, this substance being cleared extremely rapidly by the kidneys (Neuberger *et al.*, 1947). This compares with 4.1 g. in our patient, and the difference may be due to the smaller amount of phenylalanine and tyrosine in some of the vegetable proteins, which comprised 17% of the protein intake. The production of this quantity of homogentisic acid led to a compensated acidosis, as demonstrated by the normal electrolyte pattern, and an increased proportion of urinary ammonium nitrogen.

This case, which presented with the symptoms of osteoarthritis, illustrates the variety of the features resulting from the metabolic abnormality.

We wish to thank Dr. Arnold Bloom, and Professor A. Neuberger for their helpful suggestions in the study of the patient while she was under their care.

MICHAEL A. NEWTON, M.B., M.R.C.P.,
Medical Registrar, Whittington Hospital, London.*

FRANK F. RICHARDS, M.B., B.Chir.,
Lecturer, Department of Chemical Pathology,
St. Mary's Hospital, London.

REFERENCES

- Block, R. J., and Bolling, D. (1951). In *The Amino Acid Composition of Proteins and Foods*, 2nd ed., p. 107. Thomas, Springfield, Illinois.
- Garrod, A. (1908). Croonian Lectures.
- La Du, B. N. (1960). In *The Metabolic Basis of Inherited Disease*, 1st ed., p. 394, edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson. McGraw-Hill, New York.
- Zannoni, V. G., Laster, L., and Seegmiller, J. E. (1958). *J. biol. Chem.*, **230**, 251.
- Lichtenstein, L., and Kaplan, L. (1954). *Amer. J. Path.*, **30**, 99.
- Milch, R. A., Titus, E. D., and Loo, T. L. (1957). *Science*, **126**, 209.
- Neuberger, A. (1947). *Biochem. J.*, **41**, 431.
- Rimington, C., and Wilson, J. M. G. (1947). *Ibid.*, **41**, 438.
- Young, H. H. (1944). *J. Urol.*, **51**, 48.

* Now at University College Hospital, London.