the outbreak strains when both human and rabbit convalescent sera were tested by neutralization tests. On the other hand, preliminary tests by the haemagglutination-inhibition technique using immune rabbit sera show no difference between the strains. Further work is in progress on this point, but it is possible that this difference in the antigenic properties of the outbreak strains may be related to their capacity to cause recognizable outbreaks of infection.

Summary

Evidence of E.C.H.O. type 7 virus infection was demonstrated in 19 individuals in the north-east region of Scotland in 1961. Ten patients showed the clinical picture of aseptic meningitis; E.C.H.O. type 7 virus was isolated from the cerebrospinal fluid in three, and in all of them antibody studies suggested concurrent infection.

Neutralizing antibody tests showed antigenic differences between the outbreak strains and the prototype strain, but no differences were apparent when the haemagglutination-inhibition tests were used.

We should like to express our thanks for permission to refer to the records of cases under the care of the following members of the staffs of Aberdeen General and Special Hospitals Groups; Professor John Craig, Professor H. W. Fullerton, Mr. H. A. F. Dudley, Dr. W. H. Galloway, Dr. Campbell Murray, and Mr. W. Martin Nichols; and to Dr. W. A. Ross, general practitioner, Laurencekirk. We are also indebted to Professor A. Macdonald for his advice and encouragement.

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VITAMIN A IN ACNE VULGARIS

REPORT BY THE SOUTH-EAST SCOTLAND FACULTY OF THE COLLEGE OF GENERAL PRACTITIONERS*

"When a patient runs an imminent and certain risk, it is justifiable, or at least excusable, to use every remedy, as in such a case we cannot make bad worse. Still, even in such cases, our therapeutic action must be defensible in theory and by an appeal to analogy."—TROSSEAU on Experiments on Patients.

According to Unna (1894) the basic histological picture in early acne is an even hyperkeratosis of the epidermis which spreads to the openings of the pilosebaceous follicles, with the formation of comedones. Since the early histological picture resembles that found in vitamin-A deficiency, it would appear that there is some evidence to support the theory that vitamin A might be of value in the treatment of acne vulgaris.

This underlying rationale of the use of vitamin A in acne explains the many dermatological papers on the subject. One of the first reports was that by Straumfjord (1943), who treated 100 patients with 100,000 I.U. daily for periods of six months or more. Seventy-nine showed considerable improvement and only three were unimproved. Straumfjord made the point that in many cases a definite aggravation occurred early in treatment before benefit ensued. Ten years later Fell and Mellanby (1953) gave experimental support to the theory by showing that explants of embryonic chick ectoderm grown in media containing excess of vitamin A underwent suppressed keratinization as compared with control explants grown in normal media. While the control explants formed keratinizing squamous epithelium, those with excess vitamin A underwent a differentiation into mucus-secreting, often ciliated, epithelium similar to that of normal nasal muscosa.

The largest series in which vitamin A alone has been used as therapy was described by Germeraad, Vasbinder, Verbeek, and Van Der Sijde (1955) in Holland. They treated 133 cases, using 100,000 I.U. thrice daily for periods of six to nine months, and thought that the majority of these cases had been improved by the treatment. They estimated the vitamin content of the plasma at intervals and found that the best results were obtained when that level rose above 300 I.U./100 ml. They also found that oral administration was as satisfactory as parenteral and that doses of 50,000 I.U. thrice daily were sufficient to achieve this level.

The above authors and others have agreed that acne which was characterized by prominent follicular plugging in addition to the formation of comedones responded best to treatment with vitamin A, whereas the results were disappointing in the pustular and cystic types. Most trials suffered from lack of proper control cases. The place of vitamin A in therapy therefore did not appear to us to be established on firm grounds, especially as further workers —Lynch and Cook (1947) and Mitchell and Butterworth (1951)—found their results disappointing. It seemed that with a long-term and fluctuating condition such as acne there was a good case for a double-blind therapeutic trial, using an objective method of assessment to judge results. Furthermore, we wished to study the problems such an objective method might raise in general practice.

Logan (1960), analysing the records of members of the College of General Practitioners, indicated that 4.1 per thousand of the population sought advice for this condition annually and that most of these were in age-group 12–24 years, which comprised 18% of the population. A group of general practitioners would therefore be likely to see sufficient numbers for statistical purposes, and the criteria of the disease would be relatively easy to define—a very important point in any group research. Control of therapy during the trial would be simple in general practice, and the fact that there were no known cures for the condition meant that ethical objection to a double-blind trial using dummy tablets would be absent. Having a large number of observers to assess the clinical picture, however, presented difficulties; therefore it seemed wise to establish a precise method of final assessment of results, uniform for all cases in the trial. Colour photography judged by a panel of three was the method selected.

Method

The trial consisted of a comparison of the effects of tablets of vitamin A, each containing 50,000 I.U., with dummy tablets containing lactose 10 mg., starch 110 mg.,

*Recorders: Dr. J. A. D. Anderson and Dr. I. H. Stokoe.

and talc 2 mg. Three tablets were given daily with the main meal of the day for the period of the trial, and neither doctor nor patient was aware from appearance, taste, or smell which tablet was being prescribed. The patient received either the dummy or the active tablets during the whole course of the trial.

Acne vulgaris was defined as a greasy skin with blackheads and pustules or cysts of the face irrespective of whether the condition was confined to this site or not. The active dummy tablets were randomized in groups of 20, the first group being allocated to females and the second to males, and so on alternately to the end of the series. Patients who agreed to participate in the trial were selected from the age-group 14–21 years. Those who had had recent *x*-ray therapy, ultra-violet light, antibiotics, or peeling paste were excluded from the trial.

The duration of the treatment was 12 weeks and patients reported at monthly intervals to their own family doctor, who recorded his impression of the progress of the condition on a special card. The nature of intercurrent illness and the treatment were recorded and a record was kept of all patients who were excluded or who defaulted from the trial. During the period of observation local therapy was restricted to sulphurated potash and zinc lotion, *B.N.F.*

The principal method of assessment of results was by colour photography. A colour transparency was taken of the left side of the face at the beginning and end of the trial; this side was used irrespective of the extent of the rash on the other side of the face or elsewhere on the body. To ensure that photographic conditions were the same on both occasions great care was taken to use standard lighting, exposure, and film. A special portrait frame was attached to the camera so that distance and alignment were the same for the two photographs taken of each patient. These elaborate precautions were necessary to avoid different colour depths in the different transparencies due to alterations in light-reflection from the face. Female patients were requested to avoid using make-up before being photographed, and no female was photographed within one week of the start or end of her period.

At the end of the trial the photographs were compared by a panel of two general practitioners and a consultant dermatologist who recorded their opinions independently. The photographs of each patient were identified by a serial number; they were projected simultaneously from identical projectors on to identical screens so that the two photographs could be compared side by side. There was nothing to indicate to the viewing panel which of the two pictures had been taken first. During the viewing session 12 pairs of photographs were shown a second time to the panel in similar or reverse order on the screen without the fact being revealed to the viewers.

(Further details about the equipment and technique can be obtained from the recorders.)

Results

Twenty-four doctors participated in the trial and 80 patients attended for the first photograph. Eleven patients defaulted during the trial; 10 of these were males (seven on active tablets and three on inert tablets) and one was a female (on inert tablets). Two females were excluded from the trial, one because she was found to be over age and the second because she had been sunbathing in Greece halfway through the trial. Five patients were excluded because the photographs were faulty, and one other had to be omitted as the card was not returned. This gave a total of 19 patients who were excluded from the trial.

There were thus 61 patients with a photograph taken before and after a three-months trial period on tablets. The age and sex distribution of the sample at the beginning of the trial is given in Table I, which shows that there was a reasonably even distribution of active and dummy tablets among the different age-groups.

TABLE I.—*Distribution of Active and Inert Tablets by Age and Sex*

Age	Active			Inert			Total		
	M	F	Total	M	F	Total	M	F	Total
Under 17 ..	6	2	8	5	4	9	11	6	17
17–18 ..	11	7	18	11	2	13	22	9	31
19–20 ..	4	4	8	4	4	8	8	8	16
Over 20 ..	3	5	8	2	6	8	5	11	16
Total ..	24	18	42	22	16	38	46	34	80

The panel judged improvement by reduction in the number of comedones, pustules, and cysts and improvement in the texture of the skin. The opinions of the panel are summarized in Table II. Of 30 patients (15 male and 15 female) on active tablets 10 were considered to be improved; and of 31 (16 male and 15 female) on inert tablets 11 were considered to be improved. Improvement occurred in 34% of patients and these were divided almost

TABLE II.—*Effect of Treatment, Panel Opinion Based on Photography and General Practitioners' Opinion Based on Clinical Impressions*

	Panel Opinion			G.P.s' Opinion		
	Active Tablets	Inert Tablets	Total	Active Tablets	Inert Tablets	Total
Improved ..	10	11	21	24	22	46
No change ..	18	9	27	5	8	13
Worse ..	2	11	13	1	1	2
Total ..	30	31	61	30	31	61

equally between those taking active tablets and those taking inert ones. Deterioration occurred in 7% of those on active tablets and in 35% of those taking the inactive preparations, but the significance of this observation could be established only by a larger series. There was no evidence from the small numbers available that either the age or the sex of the patient affected the response to treatment.

The panel opinion was unanimous that seven patients had improved, eight were worse, and nine remained unchanged. The other opinions were based on majority decisions. It is interesting that out of 12 pairs of transparencies viewed for a second time the original assessment was confirmed in nine cases.

The practitioners' clinical opinions about improvement or deterioration in the condition are also summarized in Table II. Again a striking similarity was found between the response in the two groups of patients, suggesting that there is no difference between the effect brought about by vitamin A and that of the inert tablets.

Record cards were available in respect of 61 patients whose photographs had been compared. Family doctors recorded improvement based on clinical impression in 75% of the patients who were treated, whereas the panel, basing their opinion on comparative photography, recorded improvement in only 34% of the series.

Discussion

It is important to try to use an objective method of assessing results in the treatment of a chronic skin condition such as acne. The memories of both doctor and patient can be misleading and undue optimism is a well-known human failing when a new treatment is being carried out.

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 pyschoneurosis. 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.

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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