The accompanying table shows the details of each stage of treatment, its duration, and the changes in the clinical features of the case as each stage was concluded.

On completion of treatment the initial tests were repeated, and it was found that all those previously abnormal were now normal. Creatine in small amounts was still being excreted in the urine. The patient was discharged well on May 1, 1942, and when last seen (Oct., 1942) was still free from recurrence of the skin lesion.

Comment

The little change shown in the skin, etc., of the legs when only ordinary diet was given, and the marked improvement ending in complete cure when the diet was supplemented and the existing deficiencies were corrected, suggest that the diagnosis of pseudoscleroderma arising from multiple vitamin deficiency was correct. According to the table the most marked improvement occurred when nicotinic acid was given, suggesting that it was lack of this factor which was mostly responsible for the condition. This may be so, but whether nicotinic acid would have had such a marked action in the absence of adequate vitamin C nutrition is doubtful, as in multiple deficiencies vitamins are notoriously interdependent for their action. It is only possible to suggest that the combination of deficiency of nicotinic acid, ascorbic acid, and thiamin, in that order of importance, precipitated the pseudoscleroderma.

The slow response to treatment was not considered abnormal, as this is often a feature in multiple-deficiency states, and particularly so in lesions affecting the skin (O'Leary, 1942). Quicker results could have been obtained had all the missing factors been supplied together. The failure of the lesion to respond to replacement of vitamin C only, plus the failure of the author to observe any condition really closely resembling scleroderma—although skin thickening was often seen—in 58 old people with clinical scurvy observed over the past five years suggests that the lesion noted in association with scurvy by Pfeiffer, if really resembling scleroderma as did the case described above, was the result also of multiple deficiency, vitamin C not being the most important lack.

Changes faintly resembling certain stages of true scleroderma may result from vitamin deficiency and are not uncommonly found. The changes seen and the factors responsible are: (a) subcutaneous oedema, causing apparent skin thickening and fixation and muscle tenderness from lack of vitamin B (Eddy and Dalldorf, 1941); (b) atrophy of epidermis, papillary oedema, papillary capillary dilatation, slight oedema of the dermis, and pigmentation from lack of nicotinic acid (Eddy and Dalldorf, 1941); (c) subcutaneous haemorrhages causing thickened skin and pigmentation due to lack of vitamin C; and (d) atrophy of muscle fibres in experimental animals, due to lack of vitamin E (Pappenheimer, 1939; O'Leary, 1942).

Other records of pseudoscleroderma of nutritional origin are few. Reports of cases which might have had this origin are: (a) a lesion similar to that described in this paper in a patient in association with Sjogren's syndrome (Sheldon, 1939); and (b) a lesion in a poorly nourished woman in whom cure resulted when a good diet was given (Meakins, 1926). It is suggested that it might be more common than is thought, and, as support, attention is drawn to the reports of scleroderma appearing in patients debilitated by cancer of various organs, in some of whom it disappears when the cancer has been treated and the general nutrition improved, good food being noted to be particularly beneficial in one instance (Behrman and Forman, 1939; Bezecky, 1935).

It is not suggested that vitamin deficiency is the cause of true scleroderma, and a search has failed to reveal any example of vitamin deficiency or deficiencies causing a change which microscopically resembles the true condition. As the clinical resemblance may be very great the importance of a biopsy in making a diagnosis of scleroderma is obvious, as without it mistakes could be made and the patient given an entirely wrong prognosis and treatment.

Lastly, although it is not intended to discuss vitamin C in general, the need of this substance by healing wounds (Crandon *et al.*, 1940) is well shown by the behaviour of the biopsy in this case. The wound made on Aug. 3, 1941, when the patient was subcorbutic, showed little healing by Aug. 18, after which date the rate of healing accelerated markedly, the wound being

firmly closed by Aug. 27. This acceleration corresponded to the addition to the patient's diet of 500 mg. of vitamin C daily by mouth, and was obviously governed by it, as all other factors were unchanged.

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PNEUMONIA TREATED WITH SULPHAMETHAZINE

REPORT OF 77 CASES

BY

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During the latter part of the past winter we have treated 77 cases of pneumonia with sulphamethazine (2-sulpha-4:6-dimethyl pyrimidine), one of the latest additions to the sulphonamide group. It is built up on the same plan as sulphadiazine, with the addition of two methyl groups to the pyrimidine ring. This addition is claimed by the makers (I.C.I.) to increase the solubility of the drug and render its deposition in the kidneys unlikely. This effect was a serious disadvantage of sulphadiazine.

Of the 51 bronchopneumonias treated in the under-12 group 30 were secondary to measles, 2 to whooping-cough, and the rest primary. The ages varied from 4 weeks to 85 years. The normal dosage of sulphamethazine employed, as recommended by the makers, is 8 g. daily for an adult, given six-hourly in 2-g. doses. As children take these drugs better than adults we assumed the adult weight for the standard dose to be 8 st., and gave a fraction of this dose according to their weight—that is, a 4-st. child received half the adult dose and so on. The full dose was given for four days, and half the dose for a further two days. Plenty of fluids were administered, and oxygen tents were used as considered necessary.

We were unfortunately unable to estimate the blood concentration with these doses. All the cases responded more promptly to the drug the earlier in the disease it was given. We think the response in cases responding favourably is slower than with sulphapyridine, but the mortality was low, as only three died (4%). One 13-week-old baby with whooping-cough and bronchopneumonia was admitted on the sixth day and died four days later. Another fatal case had measles and bronchopneumonia, was admitted on the sixth day of disease, and died on the fifth day after admission. One patient with extensive bronchopneumonia—a female aged 26—survived only 12 hours after admission. Nine other cases showed no obvious response to the drug within six days, but eventually recovered.

Out of 77 patients, therefore, 65 appeared to respond and 12 did not; three of the latter died. Of those not responding, 6 cases in adults appeared to be aberrant cases of lobar pneumonia. From one of the children who did not respond a nearly pure culture of *Staph. aureus* was found in the sputum, and she developed a staphylococcal pyaemia. Not one case in the series developed an empyema.

Toxic Effects

Owing to the risk of renal blockage and urinary suppression with the related sulphadiazine, a careful watch was made on renal secretion. One child aged 2 showed almost complete sudden urinary suppression for one day. On stopping the drug the renal flow was restored within 24 hours. No crystals

were visible in the urine, which showed only a trace of albuminuria. This patient, and two others under 2 who showed no chemical or microscopical abnormalities in the urine or any suppression, developed a curious painless brawny oedema of the whole legs and arms. The tissues did not pit on pressure. The appearance of the extremities was such as is sometimes seen in children with a tendency to chilblains during cold weather. It appeared to be due to some form of circulatory disturbance. It was not due to cold, as the wards were well heated, and the condition passed off in all three cases within 36 hours of stopping the drug. All three children were acutely ill, and were being treated in oxygen tents. They had some cyanosis of the face, due to the primary disease. All three made a good recovery. We had not observed this condition previously in any patients treated with other sulphonamides. In one other case there was a transient haematuria without any crystal deposit and without diminution of urinary flow. The drug was continued in this case without any obvious ill effect.

Apart from these possible toxic effects, sulphamethazine was extremely well taken. Vomiting was entirely absent. Slight nausea in three cases did not necessitate stopping the drug. There was no mental disturbance or depression, which are such a marked feature of cases treated with sulphapyridine. Many of the patients developed good appetites during early convalescence and were able to take large amounts of food without inconvenience while still receiving the drug. The non-toxicity of the drug was especially noticeable with middle-aged and old patients. Cyanosis was not as pronounced as with other sulphonamides. Our conclusions so far are that this is the best drug we have used for pneumonia, especially for older patients.

Working in this hospital, Ormiston, Woodman, and Lewis (1942) had a very similar mortality rate in a similar series of 140 cases treated with sulphapyridine. In another series of 120 cases (Peters, Woodman, and Lewis, 1939) reported from this hospital the mortality rate was 9% with sulphapyridine. In the accompanying table we mean by "response" that the patient became afebrile and began to improve within the period stated.

Age Group	Response to Sulphamethazine in Days								No Response within Six Days		Total
	2 Days		3 Days		4 Days		5 Days				
	Br.	Lobar	Br.	Lobar	Br.	Lobar	Br.	Lobar	Br.	Lobar	
0-2	6	1	4	1	4	—	—	—	5*	—	21
2-12	6	3	9	4	5	1	1	1	—	—	30
12-40	2	3	—	3	—	—	—	2	1†	4	15
40 and over	1	2	—	2	—	4	—	—	—	2	11

* 2 died. † Died.

Summary

A series of 77 cases of pneumonia treated with sulphamethazine is reported, with a death rate of just over 4%.

The drug is extremely well tolerated at all ages, and appears to be remarkably free of serious toxic effect, especially in middle-aged and elderly patients. The results are as good as with sulphapyridine.

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Full details of the official forms of help available to local authorities in running publicity campaigns for the immunization of children against diphtheria are contained in a special brochure put out by the Ministry of Health, the Ministry of Information, and the Central Council for Health Education. This provides in handy form a complete guide for any local authority wishing to embark on, or intensify, an antidiphtheria campaign. It is pointed out that as the result of the vigorous efforts already made about 4,000,000 children have been immunized. But there are still over 4,000,000 children unprotected. The need for action, both national and local, therefore remains urgent if the aim of immunizing at least three out of every four children between the ages of 1 and 15 is to be achieved.

THE EFFECT OF INJECTIONS OF H 11 ON THE GROWTH OF MOUSE TUMOURS

BY

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In view of the account by Gye, Ludford, and Barlow (1943) of their experiments with H 11 on tumour-bearing mice a summary of tests with similar extracts which were carried out in this laboratory in 1941 and recorded briefly in the Annual Report of the British Empire Cancer Campaign, 1942, may be of value, particularly as the two neoplasms for the most part employed were different from those utilized by the above workers.

The first is a spindle-celled sarcoma, which was produced in 1934 by inoculation of dibenzanthracene into the hind leg of a mouse and has since been transplanted through 170 passages with a high percentage of successful grafts and a very small number of spontaneous regressions. Its characteristics and histology have been intensively studied (McDonald and Woodhouse, 1938), and it has been utilized in a number of investigations, including the anti-cancer properties of various chemicals (Annual Reports of British Empire Cancer Campaign, 1941, 1942), tissue-culture experiments (Jacoby, 1940), and inoculation experiments on the chorio-allantoic membrane of the chick embryo (Jacoby, McDonald, and Woodhouse, 1943).

The second type is represented by benzpyrene-induced skin epitheliomas which also have been employed on a considerable scale for testing the possible inhibitory effects of chemical and physiological substances. Spontaneous regression of these tumours is very infrequent, and the animals may survive in good general health for several months after the appearance of papillomas, so that therapeutic injections can be made over a long period. Moreover, this type of growth permits injection experiments to be started before active invasion of the underlying tissues has taken place—i.e., in the pre-malignant phase (see protocols 4 and 5)—and in a way seems more comparable to spontaneous tumours than to a grafted neoplasm after many passages.

A small number of mice inoculated with a strain of Carcinoma 63 were also therapeutically injected. This tumour material was derived from an animal kindly given by Dr. Ludford to my colleague Dr. F. Jacoby, and is presumably identical with the Carcinoma 63 described in the paper by Gye *et al.*

The Injection Material

The examples of H 11 used were: (a) A specimen kindly supplied by Mr. Thompson of the Hosa Laboratories described as of twice the concentration for normal use. (Designated in the protocols as "Hosa.") (b) Three extracts prepared according to the directions of Thompson and his collaborators (1941) from different samples of normal male urine. (Designated in the protocols as "Birmingham, 1, 2, 3.")

Animal Material

The total of tumour-bearing mice in 8 separate experiments was 104—43 with spindle-celled sarcomas (controls included), 19 with skin epitheliomas, and 22 with "Carcinoma 63" (controls included); 20 epithelioma-bearing animals served as controls for the "epithelioma test," some receiving injections of various chemicals and others no injections or saline only. Large and vigorous animals about 5 months old were used for the grafted tumours. The applications of benzpyrene had been begun when the animals were about 10 weeks old. Although the mice were not of a pure strain they were taken from the same stock of "albino-whites."

All the injections were made intraperitoneally and, in the case of the carcinoma-grafted animals, through the flank opposite to the site of the growth.

Results

A survey of the outcome of all the tests clearly indicates that the H 11 preparation has no inhibitory effect on any of

* Carried out for the British Empire Cancer Campaign, Birmingham Branch.