of marmite on her first admission (discounting the penicillin) does not rule out pernicious anaemia, since it is known that marmite, given in sufficient quantities, may contain enough folic acid to bring about a remission of that disease. As a case of pernicious anaemia was not available here to feed on gastric juice from the patient, after incubation with beef, we were unable to ascertain whether our patient actually contained intrinsic factor. The absence of neurological symptoms in this case, which had relapsed so frequently, is also perhaps against a diagnosis of pernicious anaemia, but we think the question should remain open for the present. In any event we are here only concerned with reporting the response to penicillin.

Work is continuing on the treatment of these megaloblastic anaemias with penicillin alone, and if it can be confirmed that a haemopoietic response similar to that outlined above can be obtained, then we think the field of discussion on the origin of this type of anaemia will be greatly widened.

Summary

A case of megaloblastic anaemia is reported that responded to the administration of 400,000 units of crystalline penicillin G daily for seven days. Her reticulocytes rose to 37%, and this was followed by a rise in the haemoglobin and red blood cells. No other treatment was given.

The megaloblasts had disappeared from the marrow by the fifth day of treatment and the giant stab-cells had become very much less numerous.

The response obtained to penicillin in this case in no way differed from that obtained from potent liver extract, folic acid, B_{12}, or marmite.

It is suggested that the penicillin may have produced its effects by (*a*) destroying some organism which was competing for haemopoietic substances; (*b*) removal of some haemopoietic antagonist; (*c*) preventing the absorption of glutamic acid by competing organisms, which might thus interfere with the synthesis of pteroylglutamic acid; (*d*) affecting the metabolism and excretion of some essential amino-acids.

We are indebted to the Director of Medical Services, Kenya, for permission to publish this work, and for innumerable facilities granted to us at the Medical Research Laboratory and the Nairobi Group Hospital. To the European and African nursing staff of the Group Hospital we must also tender our thanks for many facilities to meet our somewhat fastidious demands.

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The first two women doctors since 1945 to volunteer and be accepted for the U.S. Army Medical Corps reported for duty in January in the preventive medicine division of the Office of the Surgeon-General. The original law authorizing the commissioning of women doctors ended in 1947, and the new authority was established in August last. During the war of 1939–45 the U.S. Army commissioned 72 women as physicians, and 26 of these served overseas. Their duties and conditions of service are identical with those of men except that they do not serve in "forward medical installations in combat zones."

TRIAL OF A CINCHONINIC ACID DERIVATIVE IN SOME COLLAGEN DISEASES

BY

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[WITH SPECIAL PLATE]

When investigating a series of antidiuretic compounds Blanchard, Dearborn, Maren, and Marshall (1950a) suggested that a cinchoninic acid derivative, 3-hydroxy-2-phenylcinchoninic acid (H.P.C.) might be effective in treatment of conditions responding to A.C.T.H. This was prompted mainly by their discovery that when the pituitary was intact H.P.C., like A.C.T.H., reduced the ascorbic acid content of the rat adrenal.

After it had been shown by experiment on animals that toxicity was minimal (Marshall and Dearborn, 1950) a clinical trial of this preparation was made on patients suffering from conditions thought likely to benefit from a drug with A.C.T.H.-like properties (Blanchard, Harvey, Howard, Kattus, Marshall, Newman, and Zubrod, 1950b). The cases treated were 10 patients with acute rheumatic fever, 10 with the chronic variety of rheumatoid arthritis, three with bronchial asthma, and two with disseminated lupus erythematosus.

The drug was administered by mouth for periods up to 21 days, the dose being 20 mg. per kg. of body weight on the first day, and 10 or 20 mg. per kg. each day or alternate days thereafter.

Toxic effects, except for one instance of drug sensitivity (fever), were nausea, vomiting, and abdominal cramps, limited to less than 10% of patients. To obviate these effects Blanchard *et al.* (1950b) advocated that the drug should be taken after breakfast in three doses at hourly intervals with an equal amount of sodium bicarbonate. The alimentary symptoms tended to disappear with continued use of H.P.C. and the necessity to withdraw the drug did not arise.

A supply of H.P.C. was made available to Professor J. W. McNee by Roche Products, Ltd. The drug, a yellow powder, was put up in coated tablets because of its bitter flavour. The dosage used by us was 20 mg. per kg. of body weight by mouth daily, which in some instances was increased to 40 mg. In seven of the twelve cases treated administration was continued for one week, in the rest for two or three weeks. The plan of administration recommended by Blanchard *et al.* (1950b) was followed, but sodium bicarbonate was not given.

The patients treated so far comprise four with rheumatic fever, two with polyarteritis nodosa, three with scleroderma, and three with lupus erythematosus.

Rheumatic Fever

Four patients—three with acute and one with subacute rheumatic fever—were treated with H.P.C. A typical response is shown in the Chart.

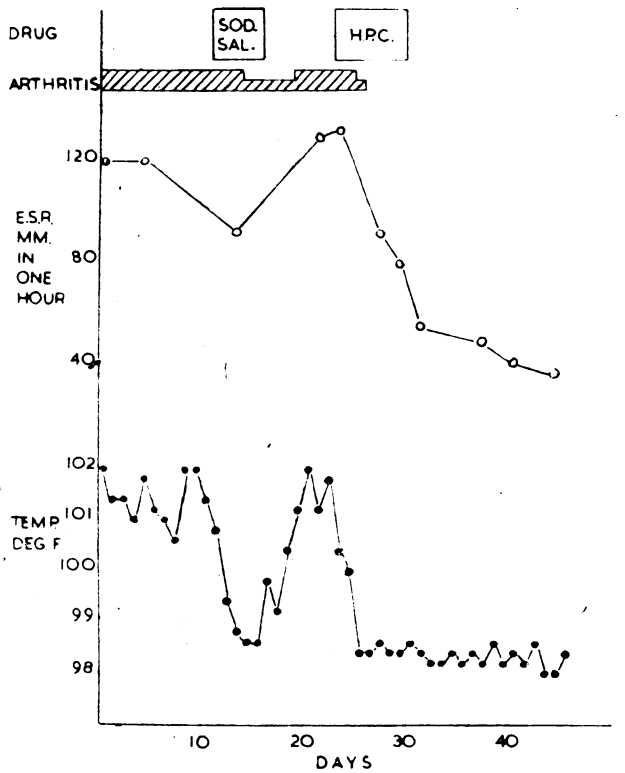

Chart showing effect of H.P.C. in rheumatic fever.

Case 1

A boy of 13 was admitted to hospital on May 30, 1950, complaining of arthritis for 24 hours after a sore throat 15 days previously. There was no history of arthritis, but he had had growing pains from time to time. On admission he was sharply ill with a temperature of 102.2° F. (39° C.) and numerous very swollen and red joints containing much fluid. There were no nodules. W.B.C. numbered 14,800 per c.mm. The E.S.R. was 94 mm. in one hour. The heart was enlarged, the apex beat being 4½ in. (11.4 cm.) from the midline in the fourth left interspace, and a systolic murmur was present at both the base and the mitral area. Blood cultures were negative.

H.P.C., 0.6 g., was given daily from June 1 to 7. Within 24 hours his temperature fell to normal, and his joints were less painful and less red. Twenty-four hours later joint effusions could just be detected; they were gone the following day. He remained symptom-free till June 15, when his temperature rose and he complained of stiffness in the joints. On June 19, although afebrile, he looked ill and once more showed swelling and redness of the carpal and tarsal joints. For another week H.P.C., 0.6 g., was given daily, with rapid relief as before. There was no further relapse. The E.S.R. (Westergren) fell from 94 mm. in one hour at the start of treatment to 56 mm. at the end. It then fell gradually and was 18 mm. six weeks later.

Case 2

A man aged 29, admitted to hospital on May 8, 1950, developed arthritis about two weeks after an attack of tonsillitis. He showed swelling of numerous joints with a moderate degree of pain and tenderness. Limitation of movement was marked. Fever was present. The heart was slightly enlarged, the apex beat being in the fifth left interspace 4½ in. from the midline. The heart sounds were very soft, and there was a short systolic murmur at the mitral area poorly conducted to the axilla. The E.S.R. was 88 mm. in one hour. Salicylates in a dose of 12 g. daily with an equal amount of sodium bicarbonate failed to control the symptoms and provoked nausea and tinnitus. Since the diagnosis was still in doubt, salicylates were omitted and penicillin, 1,000,000 units daily, was given for five days, pending the result of blood cultures. As these were negative, penicillin was stopped and aspirin given. This too caused toxic symptoms, and "disprin" was tried. This substance was better tolerated, but it, too, failed to reduce the temperature to normal. Rheumatic nodules were noted to be present at this time, and faint pericardial friction was heard at the apex for three days (May 17). All treatment was stopped for two days, and fever and joint pains increased. The E.S.R. was 70 mm. in one hour.

H.P.C., 1.2 g., was given on May 19 and continued daily for three weeks. With the first dose there was nausea and some of the drug was vomited, but no trouble occurred thereafter. Within 48 hours the temperature was normal for the first time since admission and joint discomfort very much less, being reduced to stiffness in the mornings. Joint swelling was not much affected, however, and the nodules not at all. Seven days after beginning treatment with H.P.C. there was a period of six days with fever but without return of pains in the joints. When H.P.C. was stopped the E.S.R. was 68 mm. in one hour. Throughout the period the heart size remained unaltered and the heart sounds were very soft. After H.P.C. was discontinued disprin was begun again and continued until discharge on August 19. Joint stiffness and periarticular thickening persisted for many weeks, as did the nodules, but there was no definite relapse. On his discharge from hospital the E.S.R. was still abnormal—24 mm. in one hour.

Case 3

A woman aged 43 had had acute arthritis at 16 years and again at 37. At the time of the second attack it was noted that cardiac damage had occurred. On May 7, 1950, she was admitted to hospital with multiple arthritis which had been present for two weeks. She was a stout woman who was acutely ill and had considerable fever (see Chart). Arthritis was extensive, involving hands, fingers, knees, and feet. In these areas swelling and tenderness, with limitation of movement, existed. Mitral stenosis and aortic incompetence were present. There was no heart failure. No enlargement of the heart was detected, the apex beat being 4 in. (10 cm.) from the midline in the fifth interspace. There were no nodules. The E.S.R. was 120 mm. in one hour. Her temperature was 100–102° F. (37.8–38.9° C.) and pulse rate 90–100. Salicylate, 10 g., and sodium bicarbonate, 10 g., were given daily by mouth from May 19 to 23, with the result that the temperature fell to normal and there was some improvement in the joint disability. Much nausea and some vomiting were provoked along with a degree of mental disturbance, and the drug was stopped. Fever rapidly recurred.

H.P.C., 1 g., was given on June 1 and continued daily for seven days. The temperature fell rapidly, and within 48 hours there was marked subjective improvement in the arthritis: within three days the joints were normal in appearance and there was a full range of movements. A rapid fall in E.S.R. from 125 to 48 mm. in one hour coincided with the administration of H.P.C. No relapse followed withdrawal, and she was discharged on August 3. There was no change in the size of the heart or in the murmurs previously noted. The E.S.R. was 20 mm. in one hour.

Case 4

A girl of 13 was admitted to hospital on June 5, 1950, with a history of polyarthritis for about a month and of frequent sore throats for some years. On admission there was some tenderness and limitation of movement of the right wrist and elbow and of the right hip and tarsal joints, but no swelling or redness. She had slight fever only, up to 100° F. (37.8° C.). Her pulse rate was 90–100, and the E.S.R. 62 mm. in one hour. The apex beat was 4 in. (10 cm.) from the midline in the fifth left interspace. A short systolic murmur, poorly conducted towards the axilla, was present in the mitral area. Nodules appeared on the

J. B. RENNIE, J. A. MILNE, AND J. SOMMERVILLE: TRIAL OF A CINCHONINIC ACID DERIVATIVE IN SOME COLLAGEN DISEASES

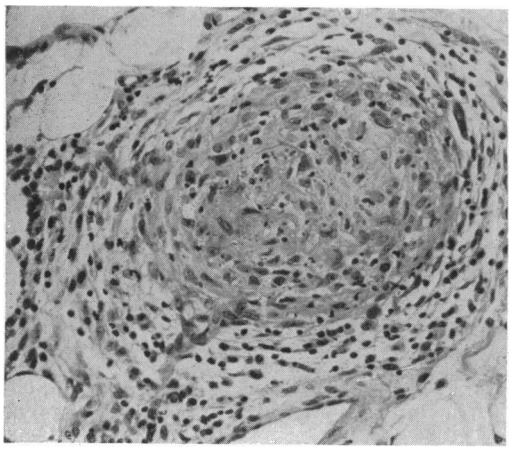

FIG. 1.—Case 6. Biopsy of deltoid muscle. A small artery is seen, the lumen of which is completely obliterated by fibroblastic proliferation. In the centre are some eosinophil leucocytes and particles of nuclear dust. The adventitia is infiltrated with inflammatory cells in which occasional eosinophil leucocytes are present. (H. & E. × 200.)

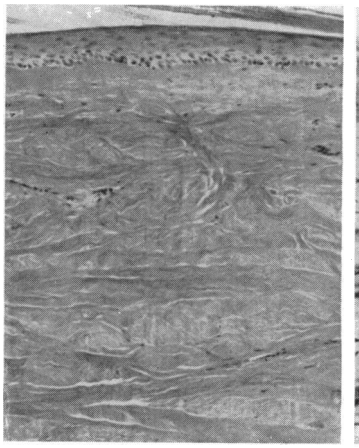

FIG. 2.—Case 7. Skin of abdomen before treatment. Note the stretched atrophic-looking epidermis. The corium is made up of dense parallel bundles of collagen with no differentiation into papillary and reticular layers. (H. & E. × 70.)

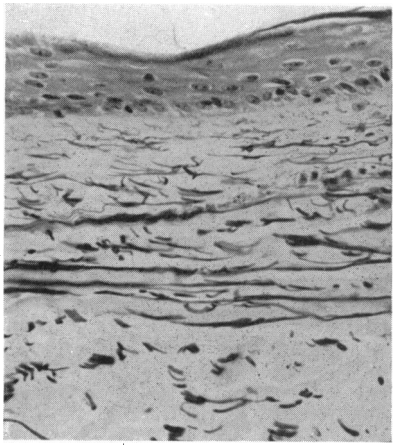

FIG. 3.—Case 7. Skin of abdomen before treatment. This section is stained for elastic fibres and shows these lying parallel to the epidermis. (Orcein. × 200.)

M. D. BABER, E. ap I. ROSSER, AND J. D. O'D. LAVERTINE: CARCINOMA OF THE CERVIX UTERI IN AN INFANT

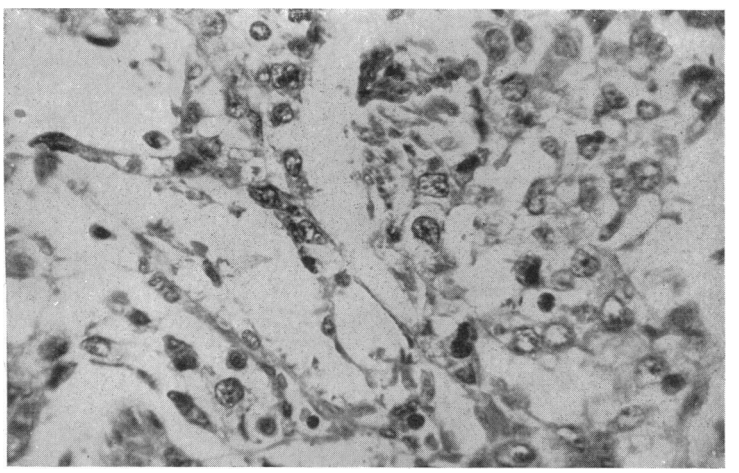

FIG. 1.—Primary growth (× 380): poorly differentiated area.

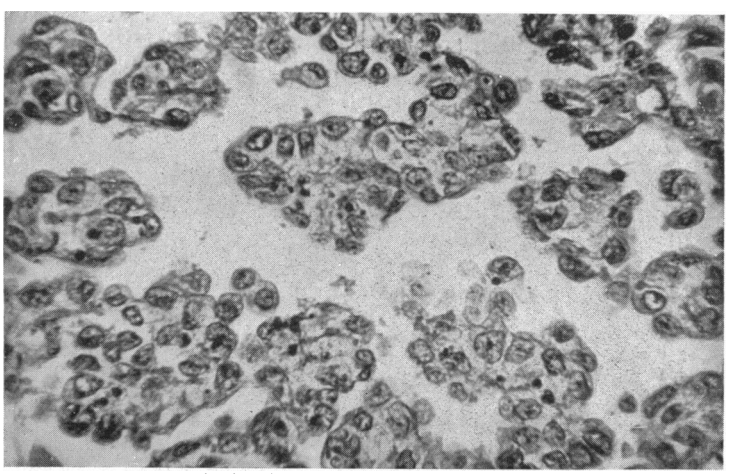

FIG. 2.—Metastasis in liver (× 380): well-differentiated papillary adenocarcinoma.

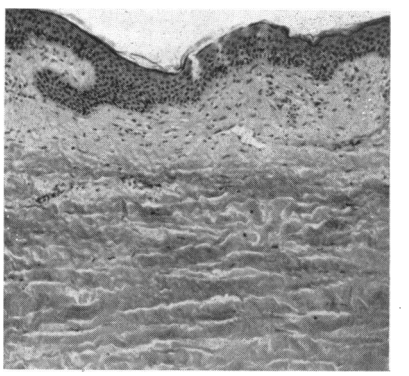

FIG. 4.—Case 7. Skin of abdomen after treatment. The epidermis is thicker and there is evidence of rete pegs. The papillary layer of the corium has re-formed. The reticular layer is still composed of dense collagen, but near the papillary layer there is evidence of breaking up and the fibres are becoming wavy. (H. & E. × 70.)

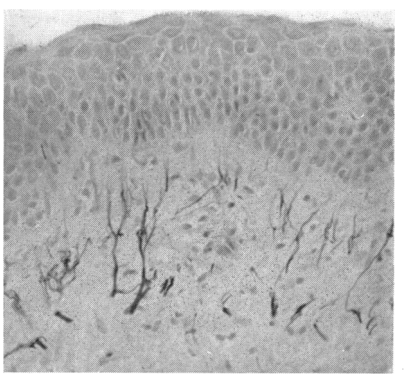

FIG. 5.—Case 7. Skin of abdomen after treatment. The elastic fibres in the upper part of the corium are seen to have assumed their normal relationship, being at right angles to the epidermis. (Orcein. × 200.)

occiput on May 9. H.P.C. was started, 0.8 g. daily, on June 10, and continued for seven days. The slight fever ceased at once and the joint pains disappeared. Three days after H.P.C. was stopped fever and joint pains recurred and additional nodules appeared on the wrists and right patella. This patient was subsequently treated with aspirin and made a good recovery.

Comment.—In these four cases, fever and painful joints were relieved. Joint swelling rapidly disappeared in two of the three patients in whom it was present. In two out of four, a fall in E.S.R. proceeded slowly and without apparent relation to H.P.C. therapy, whereas in Cases 1 and 3 a rapid partial fall coincided with the treatment. The drug did not influence the heart so far as could be judged by size or quality of sounds or murmurs. It is also noteworthy that subcutaneous nodules in two patients were uninfluenced.

Polyarteritis Nodosa

Two patients with polyarteritis nodosa were treated.

Case 5

A woman aged 63 had a sore throat in June, 1950, after which fever and anorexia persisted, followed by polyarthritis. She was regarded as suffering from rheumatism, and was treated unsuccessfully with salicylate. Penicillin and a sulphonamide were then tried, also without benefit. Blood cultures and agglutination reactions were negative. On September 2 she developed pain in the left side of the chest and was admitted to Ballochmyle Hospital in charge of Dr. A. P. Agnew. Slight cardiac enlargement and slight general oedema were noted. Fever and tachycardia were continuously present, the leucocytes being 35,800 per c.mm., eosinophils 1%, and haemoglobin 68%. Within a few days there was weakness of arms and legs, with loss of deep reflexes. Throat culture was negative and the urine was normal. Lumbar puncture gave a clear C.S.F., not under increased pressure, containing 20 mg. of protein per 100 ml. and 4 cells per c.mm. At this time the sulphonamide was stopped and streptomycin was given together with penicillin. Slurring of speech and increasing weakness of the limbs were now developing, and she was admitted to the Western Infirmary, Glasgow, on September 14.

In view of the severity of her condition H.P.C., 1 g. daily, was begun at once in conjunction with aneurin hydrochloride, 100 mg. daily, by intramuscular injection. Deterioration continued, with the development of pericarditis and extensive complete motor paralysis in all four limbs. Sensory loss was also present, but co-operation was not good enough to permit of its delimitation. Porphyrins were not present in the urine. On September 29 the white cells numbered 20,000 per c.mm., with eosinophilia of 3%. The dose of H.P.C. was increased to 1.8 g., but on September 30 she died. The clinical diagnosis of polyarteritis was confirmed at necropsy (Dr. G. B. S. Roberts), when the principal relevant findings were small infarcts in the liver and kidneys. No gross abnormality of brain or spinal cord was found. The coronary artery walls were thickened and were considered to be the seat of polyarteritis, and vessels in relation to infarcts in the liver showed similar appearances. A staphylococcal pericarditis was present. Histological examination showed the typical vascular changes in the peripheral nervous system and elsewhere.

Case 6

A woman aged 40 had been under treatment for some time for vague pains said to be rheumatic, for which she received probably 2 gr. (0.13 g.) of phenobarbitone daily for 10 days. There then appeared redness of face, body, and limbs, accompanied by puffiness, a feeling of heat, and intense itching. She was admitted to the infirmary as a case of dermatitis exfoliativa due to phenobarbitone. At that time the leucocyte count was 18,000 per c.mm. with 37% eosinophils. Within a few days the state of the skin improved, but blood and albumin appeared in the urine along with marked generalized oedema. The blood pressure began to rise from 150/90 to 200/120 mm. Hg, at which point a generalized convulsion occurred on August 24. This was considered to be a hypertensive crisis. The blood urea was 50 mg. per 100 ml.

Five weeks after admission hypertension and haematuria persisted unchanged, together with irregular fever and tachycardia. There were alimentary symptoms, nausea, vomiting, and epigastric pains which could not be explained on a uraemic basis, as the blood urea was now only 35 mg. per 100 ml. The stools contained no blood. Ophthalmoscopic examination showed in both eyes oedema of the papillomacular and peripapillary regions with fragmentation of the pigment of the choroid. Patches of exudate with soft edges and small clumps with hard edges were seen, while the retinal vessels themselves were comparatively normal. The picture was thought likely to be that of polyarteritis nodosa rather than a hypertensive or renal retinopathy (Dr. R. Leishman). On September 21 a biopsy of the right deltoid muscle was made. In one of the sections a small artery was seen to be obliterated, and in the centre were nuclear dust and an occasional eosinophil (Plate, Fig. 1). The leucocyte count was 12,200 per c.mm. with 2.5% eosinophils. The E.S.R. was 50 mm. in one hour.

Treatment with H.P.C. was begun on September 30, 1.2 g. being given daily for 17 days, increased to 2.4 g. for four days, after which it was discontinued owing to nausea and occasional vomiting. During treatment the blood pressure fell from 190/120 to 160/105. Haematuria ceased, though albuminuria still persisted, and alimentary symptoms completely disappeared along with fever and tachycardia. The E.S.R. fell from 50 to 23 mm. in one hour. Ophthalmoscopic examination on November 11 showed a completely different picture. The most prominent feature was the new development of a well-marked macular star. Retinal oedema had disappeared, as had the exudates of soft and woolly type formerly noted.

When seen in the out-patient department on November 28 the patient was very well and had gained 3 lb. (1.36 kg.) in weight. Albuminuria was slight and haematuria microscopic, while the blood pressure was 140/90 mm. Hg. The E.S.R. was 8 mm. It was stated that the vision was improving, though no change in the state of the fundi was obvious from the last examination.

Comment.—Two patients with polyarteritis nodosa were treated with H.P.C. One was very ill at the beginning of treatment, which did not appear to influence the course of the illness in any way. Regression of the disease is known to occur, and even spontaneous recovery, but in our other patient administration of H.P.C. seemed to cut short the illness and was followed by a remarkable change for the better. The blood pressure, high at the beginning of treatment, fell to normal, fever and tachycardia ceased, as did nausea, epigastric pain, and vomiting, while the lesions in the fundi regressed. At the time of writing she was gaining weight and feeling well, though the residual lesions in the macular areas had reduced visual acuity and albuminuria and microscopic haematuria were still present.

Scleroderma

After a preliminary biopsy three patients with scleroderma received H.P.C.

Case 7

A woman aged 66 was admitted to hospital on August 5, 1950. Two and a half years previously she had noted an area of skin on the back becoming "grey and stiff," associated with severe itching. This process spread gradually to the abdomen and to the thighs, so that, latterly, movement was greatly restricted and she had had great difficulty in sitting down and rising from a chair. Walking was done

with the aid of a stick and in a semi-stooping position. She had been for long periods in hospital, but had not benefited. She was a stout woman with hypertension. There was extensive scleroderma of the back, abdomen, thighs, and legs, enclosing in the popliteal space an indolent ulcer with widespread secondary infective dermatitis. Barium swallow revealed no oesophageal lesion. Biopsy from the skin of the abdomen (Plate, Figs. 2 and 3) showed a rather atrophic epidermis with loss of the rete pegs, the distinction between the papillary and reticular layers of the corium being lost, the entire corium being occupied by thickened sclerotic acellular bundles of collagen. The staining reactions of this collagen showed some deviation from the normal, tending to take up a yellowish-brown colour when treated with van Gieson's stain. In appropriately stained sections the elastic tissue of the corium could be seen stretched out and lying parallel to the epidermis.

Treatment with H.P.C., 1.8 g. daily, was given from August 11 to 17 without immediate effect on the lesion, but by August 30 it was noted that all sclerodermatous areas were less rigid and less glazed, and showed a tendency to become slightly scaly. The broken-down area and the dermatitis on the leg had regressed remarkably. By September 18 the patient's movements were restored to normal. Save for some scattered areas of brown pigmentation, all the affected parts of the skin appeared to be almost normal in consistence and colour. Biopsy (October 3), from an area near the first, showed a considerable change (Figs. 4 and 5). The rete pegs had reformed, the papillary layer of the corium was recognizable, and in it patent capillaries were evident. The collagen of this layer showed normal staining properties. The reticular layer was still composed of dense sclerotic collagen, but in its more superficial part the fibres showed a tendency to loosen and become wavy once more. An interesting feature was the return of the normal arrangement of elastic fibres running at right angles to the epidermis in the papillary layer of the corium. The clinical improvement had been maintained when the patient was last seen on November 2, and she was naturally overjoyed with the return of mobility.

Case 8

A girl aged 11 was admitted to hospital on July 3, 1950. Three months earlier an area of skin on the left leg had become firm and shiny. There was no systemic disturbance. She was a well-nourished girl, with no complaint save for a patch 4 by 2 in. (10 by 5 cm.) on the outer aspect of the left leg just below the knee. It was white, smooth, and very hard. There was no heliotrope edge. The E.S.R. was 4 mm. in one hour. The histological features of the lesion before treatment were those of active scleroderma, the distinction between papillary and reticular layers of the corium being lost, the affected area being occupied by swollen collagen bundles with altered staining properties. At the junction with normal tissue a band of lymphocytic infiltrate was present.

H.P.C., 1 g., was given daily from July 11 to August 2. At the end of that time the patch was unchanged in size, but the skin was much softer and could be wrinkled. In colour it was now brown. On August 3 the histological picture had altered considerably. The arrangement and tinctorial properties of the collagen of the upper two-thirds of the corium were almost normal. In the deeper part, however, slight thickening and hyalinization of the bundles were discernible and traces of inflammatory infiltrate were still present. On October 3 the lesion was still of the same size, but was harder than on September 1. Biopsy showed that the sclerodermatous process was again evident, and, though not so prominent as in the initial biopsy, it was more marked than in the second. The clinical picture showed no further alteration on October 30.

Case 9

A woman aged 51 was admitted to hospital on August 4, 1950. About two years previously the skin over the breasts and part of the chest and abdomen became very hard, itchy, and grey. She was found to be a well-nourished and healthy woman with lesions of scleroderma on the breasts, upper abdomen, antecubital fossae, left arm and forearm, anterior aspects of the thighs and shins, and the dorsum of the right foot. In these areas the skin was pale, smooth, and very hard, with atrophic scarring in places and a faint irregular heliotrope margin on the breasts. There was some brownish pigmentation on the chest and abdomen, but no scaling. A barium swallow showed no evidence of an oesophageal lesion. Biopsy performed on a lesion on the flexor aspect of the left wrist revealed the typical histological picture of active scleroderma.

H.P.C., 1 g. daily, was given from August 11 to 17. Within three days itching was said to be gone, and at the end of the time the lesions were much softer. On August 18 the histological picture was basically similar, though sections cut and stained simultaneously with those of the first biopsy showed a slight but definite improvement as evidenced by less thickening and hyalinization of the collagen bundles, with more normal tinctorial properties. On August 24 clinical improvement was very marked, the abdominal skin in particular being almost normal save for brownish pigmentation. The breast lesions had improved less, but were softer than before. On October 3, however, there was a definite relapse, the lesions appearing larger and firmer, and a heliotrope margin was again obvious in the more active lesions on the breasts, particularly the left. Sections showed the lesions to have advanced somewhat, the thickening and hyalinization of the collagen bundles being more marked. A band of inflammatory infiltrate suggested renewed activity. On October 31 the clinical condition showed no change.

Comment.—Clinical improvement, supported by histological evidence, occurred in all three patients with scleroderma. It was striking in one case, even after only one week of treatment, and, so far, it has continued. In the other cases improvement occurred up to a point, but was followed by relapse, clinical and histological.

Lupus Erythematosus

Of the three patients with lupus erythematosus two (Cases 10 and 11) were of the chronic discoid type, and another (Case 12) is best described as of subacute disseminated type.

Case 10

A man aged 39 had had a rash on his face for six years and dyspepsia for one year. Bismuth, gold, and arsenic had been used unsuccessfully for the lupus erythematosus. The lesion on September 13, 1950, was symmetrical and almost batswing, with distribution over the nose, cheeks, and malar and zygomatic regions. Both pre-auricular regions were affected, and scarring was evident in these sites. The lesions were florid, and there were some at an earlier stage on the mid-forehead and lower lip. Biopsy showed the histological changes typical of lupus erythematosus. The only other abnormality was a duodenal ulcer, the presence of which was confirmed by a barium meal. The E.S.R. was 4 mm. in one hour. The white cells numbered 6,400 per c.mm., with 1% eosinophils. The plasma proteins were normal.

In view of the duodenal ulcer, H.P.C. was given cautiously, with an initial dose of 0.2 g. on September 20. No increase of dyspepsia followed this or the subsequent administration of 1.2 g. of the drug daily. On September 27 the lesions were less florid and showed fine scaling, and the malar lesions had small areas of central and marginal pallor. A biopsy, however, revealed no appreciable change in the histological features. H.P.C. was stopped on October 4, at which time the more peripheral parts of the lesions had become paler and much less noticeable. The patient was discharged from hospital on October 9, with the rather reserved conclusion that the

slight clinical improvement had been maintained. On October 23 the condition had reverted to what it had been before H.P.C. was given. Further biopsy showed no histological change from the state existing before treatment.

Case 11

A woman aged 40 had had a rash on her face for seven years, but was otherwise well. On the face there were two irregular pale red rather scaly patches—one on the bridge of the nose extending to the left cheek, the other, smaller, on the right side of the chin. The E.S.R. was 5 mm. in one hour, and the white cells numbered 4,200 per c.mm. The plasma proteins were normal. Skin biopsy showed the histological changes typical of chronic lupus erythematosus. H.P.C., 1.2 g., was given daily for seven days. At the end of a week, on October 26, 1950, there was on the whole little change, though the lesions were perhaps less florid and scaling perhaps a little more pronounced. On November 5 the lesions on the chin were less red and showed some scarring. There was no further change in the lesions on the cheek. A further biopsy has not yet been done.

Case 12

A woman aged 31 had developed a rash on the face nine years earlier. This had persisted, but, in addition, she had had occasional patches of similar appearance on the forearms and the tips of the fingers. From time to time she had had swollen joints and "fibrositis." The menses had lasted up to 11 days, producing anaemia with breathlessness on exertion for some time. Admission to hospital on September 25, 1950, was precipitated by pain in the right side of the chest on coughing and deep breathing, coming on four days earlier. There had been initial shivering, and cough was frequent, with a profuse thick yellow sputum. She was acutely ill, with a temperature of 102° F. (38.9° C.), dyspnoea, and cyanosis. The sputum was purulent, yellow, and contained staphylococci on culture. Physical signs indicated patchy consolidation, most marked at the right base. Rapid improvement followed the use of penicillin. On October 9, seven days after penicillin was discontinued, the skin lesions were as follows: extensive patches were present on the face, with batswing distribution, and also on the forehead; single small lesions were also present on both forearms; the colour was a deep dull red owing to considerable telangiectasia; and a moderate degree of stippled scaling was noted on the areas above the eyebrows and across the malar region. Biopsy showed the histological changes characteristic of lupus erythematosus. The leucocyte count was 9,800 per c.mm., with 5% eosinophils. The E.S.R.—84 mm. in one hour on admission—was 50 mm. The haemoglobin was 9 g. per 100 ml. Plasma albumin was 4.68, globulin 3.81, and fibrinogen 0.46 g. per 100 ml. A radiograph of the chest showed no abnormality in the lungs except a healed tuberculous focus at the left apex.

H.P.C., 1 g. daily, was given from October 10 to 19, when the amount was increased to 1.8 g. On this treatment vomiting occurred on several occasions, and the drug was discontinued on October 23. Vomiting then ceased. The skin lesions were paler, particularly on the forehead. On October 27 fever returned, though no cause for this could be found. A further radiograph of the chest revealed no abnormality and no change in the tuberculous lesion already noted. The E.S.R. was 50 mm. in one hour. If anything the face lesions were worse. A further biopsy on October 31 showed no change in the histological features. On November 6 the skin lesion on the face showed small areas of pallor at the margins and also centrally, as if some regression was taking place. Fever continued, though the patient did not appear to be acutely ill.

Comment.—All that can be said concerning these cases of lupus erythematosus is that during administration of H.P.C. the lesions were thought to be less florid and to show some slight evidence of regression; but this was not confirmed histologically, nor was it maintained.

Discussion

In our series, four patients suffering from rheumatic fever were given H.P.C. Rapid disappearance of joint pains and fever followed, confirming the findings of Blanchard *et al.* (1950b), who reported similar results in 10 patients. In neither series was a complete fall of the E.S.R. to normal associated with administration of the drug. Relapse followed withdrawal of H.P.C. in three patients of Blanchard *et al.* This occurred twice in our series, the symptoms being again, and finally, relieved by a further course of the drug once and by aspirin once. In our small series of patients treated, H.P.C. would seem to be at least as good as sodium salicylate and less toxic.

Of the two patients with polyarteritis nodosa, rapid and striking improvement in one coincided with the administration of H.P.C. While spontaneous regression is known (Miller and Daley, 1946), Herson and Sampson (1949) found that four patients who showed lesions in the fundi all died within a few weeks.

Compared with the notable results obtained in rheumatic fever, the response in scleroderma is all the more striking when it is recalled how ineffective many therapeutic agents, ranging from local therapy of various types to partial parathyroidectomy, have proved in the past. It is interesting that Bayles *et al.* (1950) have reported that even A.C.T.H. failed to produce change in the histological appearances, and only very moderate and temporary clinical improvement. Using H.P.C., we have seen one patient who showed marked clinical improvement that continued after cessation of the drug, which was given for one week only. Both from the clinical and from the histological aspects this patient was in the late burnt-out stage of the disease, and, though the papillary layer of the corium has re-formed, the reticular layer is still markedly sclerotic. It is difficult to realize that the return to normality of a layer of connective tissue less than 1 mm. in thickness should be associated with such marked clinical improvement. Our experience with the other two cases of active scleroderma, in which there was clinical and histological evidence of improvement during and shortly after treatment, followed by continuance of the disease process some weeks later, would suggest that H.P.C. is more effective in the late burned-out stage of the disease. The question whether H.P.C. causes reversion of the changes produced by the disease process or acts against the causative factors can be settled only by further study. It may be, however, that some variation in the use of the remedy is required in the active form.

Our experience with three patients suffering from lupus erythematosus was disappointing and in accord with that of Blanchard *et al.* (1950b) in two patients. It should be noted, however, that in our cases the disease was confined to the skin, while in those of Blanchard and his colleagues visceral manifestations were present. Some authorities (Baehr, 1949) consider lupus erythematosus of the skin and lupus erythematosus with visceral manifestations in addition to be different conditions, a hypothesis to which we do not subscribe.

Toxic effects were few. As reported by Blanchard *et al.* (1950b) nausea was not uncommon on the first day of treatment, but it ceased to be troublesome thereafter. In our group vomiting occurred in three patients

—in one on the first day and in two after the dose had been greatly increased. Slight looseness of the bowels, not severe enough to call for cessation of treatment, was noted in four patients. In febrile patients with concentrated urine, an appearance highly suggestive of bilirubinuria was encountered and a positive reaction was obtained with the methylene-blue and nitric-acid tests. This result was found to be a fallacy, however, as similar reactions were given with a suspension of H.P.C. in water.

Summary

A cinchoninic acid derivative, 3 - hydroxy - 2 - phenyl - cinchoninic acid (H.P.C.), has been used in a small series of patients.

Fever and acute arthritis were speedily relieved in rheumatic fever.

Results in polyarteritis nodosa were equivocal.

The most striking effects in our series were obtained in three patients with scleroderma, a disease hitherto not responsive to any known treatment. Improvement occurred in all cases, as shown by the histological examination of biopsy specimens obtained before and after treatment. The results were striking and have so far been maintained in one case, but were only temporary in two.

Very slight and inconstant improvement followed the administration of H.P.C. in chronic lupus erythematosus, but was not confirmed by histological examination.

Toxic effects were infrequent and less severe than those which may follow the use of sodium salicylate, and consisted in slight nausea, diarrhoea, and, more rarely, vomiting.

We are grateful to Professor J. W. McNee, whose personal association with the original group of workers in Johns Hopkins Hospital, Baltimore, made this investigation possible, for his kind offices in arranging the necessary supplies through Dr. F. Wrigley, of Roche Products, Ltd., and for his continued interest, help, and advice.

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The new flying-spot microscope is a topsy-turvy instrument invented by Professor J. Z. Young and Mr. F. Roberts (*Nature*, February 10, p. 231). It works backwards. Normally light passes through a specimen into the objective and eyepiece, and the observer applies his eye and scans the field of view, looking at whatever interests him in it. In the new microscope, a narrow beam of light enters the eyepiece, passes down the tube and out through the objective, to be concentrated on a tiny bit of the specimen, through which it is filtered to a multiplier photocell—which corresponds to a stationary eye which is letting the light scan the field of view for it. A very bright light from a television-type cathode-ray tube provides the light spot, which rapidly and systematically scans the whole cross-section of the eyepiece; the microscope converts this to a rapid point-by-point scan of the specimen under the objective, and the photocell, recording the point-by-point change in brightness, builds up on a further television screen a vastly enlarged picture of the specimen. This new instrument promises greater resolution, greater contrast without staining, ultra-violet "vision," and quantitative analysis of the specimen.

SIDE-EFFECTS OF CHLORAMPHENICOL AND AUREOMYCIN, WITH SPECIAL REFERENCE TO ORAL LESIONS*

BY

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[WITH SPECIAL PLATE]

With the growing use of antibiotics the side-effects of treatment with these drugs are becoming more important. They are negligible with penicillin, but are of some significance with streptomycin. They are more frequent with the use of chloramphenicol and "aureomycin," though they are not of a serious nature. The subject has been briefly mentioned by various authors, but a more comprehensive study has been made by Harris (1950). As the use of chloramphenicol and aureomycin is rapidly increasing, a survey of these side-effects seems to be justified. The frequency and intensity of oral changes also give a unique opportunity of studying the mechanism of some common oral lesions. Recently Williams (1950) described 12 cases of severe oral lesions in a group of approximately 200 patients treated with chloramphenicol. Chloramphenicol and aureomycin (Tomaszewski, 1951) also cause the disappearance of the red fluorescence of the tongue which is seen in normal people and which is due to porphyrin production by bacteria.

This survey has been based on observations of 126 cases treated with these two substances in various wards of the Royal Infirmary of Edinburgh.

The Investigation

Clinical observations were made on the side-effects of chloramphenicol and aureomycin in patients suffering from various infective conditions. In each case bacteriological examination showed that the pathogenic organism was sensitive to both substances.

To investigate the immediate effect of the antibiotics on the bacterial flora and epithelium of the tongue, scrapings of the tongue were made every two or three days in all cases before, during, and for one to three weeks after cessation of treatment. The tongue was scraped vigorously with a sterile slide several times from as far back as possible, and the material ground by means of another slide to make an even layer. After heat fixation the film was stained with Gram or with other stains when necessary. In a number of cases cultures were made on Sabouraud's medium for identification of fungi and on broth and agar for identification of bacteria.

Dosage and Method of Administration.—Both antibiotics were given orally in capsules of 250 mg. Usually two capsules, sometimes more, were administered every six hours. Seventy patients (30 males and 40 females) received chloramphenicol, and 56 (32 males and 24 females) received aureomycin. The total amount of chloramphenicol given to any one patient varied from a few grammes to 96 g.; the average dose was 32 g. Aureomycin was usually administered for a shorter period, the highest total amount being 68 g., with an average dose of 28 g.

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