In addition to the deficiency of vitamin B₁ the temporary presence of hyperkeratosis and of some darkening of the skin suggest some deficiency of vitamin A and of nicotinic acid. Both signs regressed completely after cure of the vitamin-B₁ deficiency and the taking of a normal diet. There were never any signs of riboflavin deficiency.

ADDENDUM.—During 1951 it became obvious that constrictive pericarditis had developed. In consultation with Professor I. G. W. Hill and Mr. M. Fallon it was decided to carry out pericardectomy, which was done on June 5, 1951. The patient made an uneventful recovery, and is now (January, 1952) attending school once more. Vitamin supplements were continued until the time of operation. Tuberculous tissue was found in the parietal pericardium removed at operation.

Summary

A case of multiple vitamin deficiency presenting the clinical picture of acute beriberi is reported in a patient suffering from polyserositis, possibly of tuberculous origin.

It is suggested that the toxic process causing the polyserositis also produced the beriberi symptoms.

No similar case has been discovered in the British literature.

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GRANULOMATOUS ULCER OF THE NOSE TREATED WITH CHLORAMPHENICOL

BY

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Some 35 cases of progressive granulomatous ulcers of the nose, face, and palate of unknown aetiology have been reported since 1896, when McBride first described a case of rapid ulcerative destruction of the nose and face. The literature on the subject has been reviewed by Stewart (1933a), Hoover (1941), Hargrove *et al.* (1946), and Williams (1949). No curative treatment has as yet been discovered; the course of the disease is slowly progressive, ending fatally in most cases. There have been only four reports of recovery. Woods's (1921) second case was healed after implantation of radium needles, and M'Arthur (1925) used x-ray therapy successfully. Schütz (1938) is quoted by Hoover as having reported a spontaneous cure, and Hoover himself

described an atypical case which recovered. Since the advent of antibiotics there have been reports by Hargrove *et al.* (1946) and Williams (1949). In the case described by Hargrove *et al.* penicillin appeared to control the spread of the lesion, but the patient died of pneumonia. In Williams's first case the patient died from exhaustion despite intensive treatment with penicillin, and penicillin-resistant staphylococci were cultured on numerous occasions from the ulcerated area on the nose, and from other lesions which developed on the arms and legs. The other two cases described by Williams (1949) were also fatal, but the cause of death was stated to be a lymphoma in one case and periarteritis nodosa in the other. The following case of this rare condition is considered worthy of record, as a penicillin-resistant staphylococcus was isolated repeatedly from the ulcerated area and treatment with chloramphenicol controlled the infection and resulted in healing of the ulcer, "aureomycin" previously having failed to do so.

Case Report

A married woman aged 35, employed as a part-time assistant nurse at the Sheffield Royal Infirmary, underwent an operation for submucous resection of the nasal septum on June 26, 1950. The operation was successful in relieving her nasal obstruction and she appeared to recover satisfactorily. On August 10, however, she developed a painful pustule in the left nostril, and was treated with penicillin cream locally and procaine penicillin systemically—600,000 units daily for 10 days. By this time an ulcer extending from the floor of the left nostril to the upper lip was present. She was referred to the skin department on September 4. She was not taking drugs.

Examination revealed an ulcer spreading from the floor of the left nostril to the ala nasi and to the upper lip. The ulcer was covered with a leathery black crust, and the spreading edge was raised and showed firm induration extending 1 cm. beyond the visible margin. At the edge of the crust there were small vesicles. The left cheek and lower eyelid were swollen and oedematous. The regional lymph nodes were not enlarged. Though the ulcer was painful she did not complain of constitutional symptoms and was not febrile. The ulcer was presumed pyogenic in origin, but investigations were carried out to exclude diphtheria, syphilis, anthrax, actinomycosis, and the possibility of an underlying foreign body. No foreign body was found in the nose. Blood Wassermann and Kahn reactions were negative. Radiography of the sinuses and bones of the face and teeth showed no abnormality. A blood count gave 5,000 white cells per c.mm. (52% polymorphs, 38% lymphocytes, 5% monocytes, 5% eosinophils).

Culture of aerobic and anaerobic swabs from the nose and ulcer yielded a mixed growth of a haemolytic streptococcus and *Staphylococcus pyogenes*, and a corynebacterium which was later proved non-virulent to guinea-pigs. No anaerobic streptococcus was isolated. The staphylococcus was found to be sensitive to 1,000 units of penicillin per ml., 500 µg. of streptomycin per ml., 6 µg. of chloramphenicol per ml., and 0.375 µg. of aureomycin per ml. In view of the continued spread of the ulceration the patient was admitted to the ward on September 9 and given aureomycin 250 mg. three-hourly, and applications of saline to the ulcer. On September 14 the ulcer had ceased to extend but showed no sign of healing. Repeated cultures from inside the nose and from the ulcer revealed a *Staph. pyogenes* with the same sensitivity to the antibiotics as above. It was at this stage that a diagnosis of so-called malignant granuloma of the nose was first considered. In view of the grave prognosis if this diagnosis was correct and the success of radiotherapy in the past, superficial x-ray therapy, 200 r, was given to the upper lip and the patient was transfused with 2 pints (1.14 litres) of fresh blood.

The aureomycin was stopped, as it was thought to have had little effect, and sulphadimidine was tried. Within two days it became obvious that the ulceration had been controlled by the aureomycin, since the indurated area rapidly extended and the ulcer spread to the left ala nasi. Aureomycin, 250 mg. three-hourly, was recommenced on

FIG. 1.—The condition on September 21.

FIG. 2.—Photograph taken on September 28.

FIG. 3.—Photograph taken on December 27.

September 19, the dosage being raised to 500 mg. three-hourly two days later, when it was found that the serum aureomycin was only 0.75 μ g. per ml. Within twelve hours the crusts began to separate and the induration and oedema lessened (Fig. 1). On September 25 the serum aureomycin had risen to 2 μ g. per ml., but the most recent culture taken from beneath the crust still revealed a *Staph. pyogenes* which was sensitive to 1.5 μ g. of aureomycin. On the 26th the aureomycin was increased to 750 mg. three-hourly, and a solution of aureomycin in water, 1,000

μ g. per ml., was applied on gauze to the surface of the ulcer. Despite the high dosage the serum aureomycin did not rise above 2 μ g. per ml. The ulcerated area had by now improved, since the main slough was separating and the inside of the nose appeared healed, but there was still slow extension down the lip and over the ala nasi (Fig. 2).

By October 17 the condition appeared stationary, and, in view of the greater ease with which high levels could be obtained in the serum, treatment was changed to chloramphenicol, 1 g. followed by 0.5 g. three-hourly. During the few hours at the change-over of treatment the left side of the face became more oedematous, closing the left eye, and the edge of the ulcer became more red and painful. Within 12 hours these signs had subsided and the ulcer looked more healthy than at any time previously. A further exposure to x rays, 100 r, was given on October 24. Next day the serum chloramphenicol was 25 μ g. per ml. During the next few days the oedema and induration of the face subsided and the ulcer healed steadily. Numerous cultures taken from the nose and surface of the ulcer were sterile. By November 16 only one small scab remained. The chloramphenicol was stopped and the patient was discharged home on the 18th, but was kept under observation as an out-patient.

On November 28, after a common cold, the oedema of the left side of the face returned and induration reappeared at the edge of the scar, together with several superficial pustules. Chloramphenicol, 0.5 g. six-hourly, was started at once. A culture taken from the pustules before treatment was begun showed *Staph. pyogenes* which was penicillin-sensitive, but in view of its previous success chloramphenicol was continued. The slight recurrence was cleared within a week, but the drug was given until January 4, 1951. Since then she has remained well and is not grossly disfigured, though the scar has retracted her upper lip (Fig. 3). It is noteworthy that throughout the long illness her temperature never rose above normal and her white cell count was never above 6,000 per c.mm., also that no toxic effects arose from the high dosage of antibiotics which were given over a long period.

Discussion

Sensitivity to Antibiotics.—The estimations of the sensitivity of the organisms to aureomycin and to chloramphenicol were carried out by inoculating serial dilutions of the standard antibiotics in phenol-red-serum water (May *et al.*, 1947) with a 1/10 dilution of a 24-hour broth culture. The tube which just did not show growth was taken to be the least concentration of the antibiotic to which the organism was sensitive. The antibiotic content of the patient's serum was estimated by comparing serial dilutions in phenol-red-serum water with standard dilutions of the antibiotic, using *Bacillus cereus* (Lederer No. 5) as the inoculating organism. In view of the instability of aureomycin in a solution of pH 7.6 at 37° C. it may be that the organisms tested were actually more sensitive than the *in vitro* tests showed. However, this was not borne out by the progress of the case under treatment.

Diagnosis

The clinical features of the present case correspond very closely with those previously published under the names of malignant granuloma of the nose, progressive lethal granulomatous ulceration of the nose, and chronic infectious granuloma of the nose. Photographs of Lierle's (1942) case are so similar to our case that they could easily be confused. It was perhaps fortunate that the patient, being a hospital employee, was seen at a very early stage in the disease, when it appeared to be an infection and not a neoplasm, such as might have been diagnosed if the ulcer had penetrated the tissues more deeply. For that reason, and the risk of extending the infection, a biopsy was not performed.

Aetiology

The pathological changes in all the cases previously described have been those of areas of necrosis surrounded by a zone of new granulation tissue and a zone of infiltration with inflammatory cells, mainly lymphocytes, with an occasional giant cell. Hargrove *et al.* drew attention to a state of obliterative arteritis affecting the blood vessels beyond the infiltrated area. Stewart (1933b) reviews 10 cases, and in summing up the findings says: "The disease is not one of formation but of destruction." He also draws attention to the complete absence of resistance of the patient to infection. The course of the present case excluded a malignant growth, since the radiotherapy given was not of such dosage as to control a neoplasm. The disease must then be ascribed either to an organism not yet discovered or to an unusual tissue response to infection with known pyogenic organisms.

We believe that the staphylococcus which was found so consistently in the lesion in our case played a prominent part in the cause of the ulceration and was not just a secondary invader. The spread of infection was controlled by aureomycin—rapid extension occurring when the antibiotic was stopped—and during the change-over of treatment to chloramphenicol. When adequate doses of chloramphenicol were given the staphylococcus could not be isolated from the lesion, and healing continued. The slight recurrence was due to infection with a staphylococcus of different sensitivity to antibiotics, and was therefore presumably a fresh strain. This suggests that the granulomatous overgrowth is a non-specific reaction to staphylococcal infection and not to any one particular strain of the organism. Such a theory would explain the occurrence of two attacks separated by an interval of 23 years, as occurred in Hoover's Case 3 and in Lierle's case when a recurrence was precipitated by a blow on the nose. Reinfection with a rare organism would be too great a coincidence. The absence of regional lymph-node enlargement, of leucocytosis, and, in our case, of pyrexia, suggests a failure of the defence mechanism.

That staphylococci are capable of producing indolent inflammatory lesions of the skin has long been known—this is perhaps best characterized by acrodermatitis perstans of Hallopeau; and the common pyogenic granuloma is a good example of exuberant granulation tissue stimulated by staphylococcal infection. Of 17 published cases in which bacteriological findings are given, staphylococci either alone or with streptococci were found in 15; although staphylococci can be isolated by nasal swab from many people, this finding is compatible with our theory.

Summary

A case of progressive granulomatous ulceration of the nose and face is described.

A penicillin-resistant *Staph. pyogenes* was isolated from the lesion, at first in combination with a haemolytic streptococcus and an avirulent corynebacterium; later the staphylococcus was obtained in pure culture.

Aureomycin prevented an extension of the infection, but a staphylococcus sensitive to the drug *in vitro* could still be recovered from the lesion.

Chloramphenicol produced a gradual but complete recovery, with coincident disappearance of the staphylococcus from the ulcer.

The aetiology of the condition is discussed and the suggestion put forward that it is a non-specific but unusual response to staphylococcal infection.

It is suggested that chloramphenicol may be as good as, if not superior to, aureomycin in the treatment of staphylococcal infections.

We should like to express our thanks to Mr. J. H. Cobb for his co-operation and for drawing our attention to the previously published work on the subject.

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PURPURA AND PANCYTOPENIA COMPLICATING ARSENOTHERAPY

BY

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Purpura and other blood disorders are rare complications of the treatment of syphilis by organic arsenicals. The possibility that these drugs might be responsible for the purpuric manifestations was suggested by Labbé and Langlois (1919) only nine years after their introduction. The first to be incriminated was arsphenamine, and Loveman (1932) described 14 cases in the literature up to that date, and added one case of his own which showed a pancytopenia, with thrombocytopenic purpura, agranulocytosis, and aplastic anaemia. Falconer and Epstein (1940) described eight of their own cases of purpura occurring during arsenical treatment. All the organic arsenicals employed in the treatment of syphilis have been suspect, but neoarsphenamine has been involved more often than any other—in part, perhaps, because of its more widespread use. "Mapharsen" was introduced in 1936, but purpura associated with this form of arsenical has been relatively uncommon. However, Wintrobe (1946) mentions having seen three cases, and one further case was reported by Schwartz and Vonder Heide (1945).

Though these complications of arsenotherapy are rare, four cases were admitted to the Royal Victoria Hospital during a period of nine months. These cases had a similar clinical picture but somewhat dissimilar haematological findings, and three ended fatally. These cases are thought worthy of record.

Case 1

A married woman aged 30, with one child aged 8, was first seen by her doctor in July, 1948, having a sore on the vulva. This was treated with penicillin ointment locally and a sulphonamide by mouth; her blood was serologically positive for syphilis. She was referred to the V.D. out-patient department, but refused examination. She was seen again in August, when she had developed a copper-coloured rash, which had been noticed for one day. It was distributed over the chest and abdomen, and to a less extent on the arms and inner sides of the thighs. The cervical and inguinal lymph nodes were enlarged. A small ulcer present on the vulva showed *Treponema pallidum* on dark-ground examination. Her Kahn reaction was + + + +, W.R. + +, and Dreyer reading 108. She denied extramarital intercourse, but stated that her husband, who was in the Army, had been home on leave in May of that year.

Penicillin treatment, 3,000,000 units in 10 days, was given. This was followed by courses of combined bismuth and arsenic injections. Over a period of somewhat less than a year she received 3 g. of bismuth, 0.86 g. of mapharsen, and 7.2 g. of neoarsphenamine. Serological tests for syphilis were negative in January, 1949. During the third course of