

cut surface of the tumour showed areas of marked softening and necrosis (figure 2, plate XX), and on squeezing a purulent fluid oozed out. The main bronchi were cut open, but the tumour had apparently no connection with them. The tumour had eroded the first, second and the third right ribs and caused pathological fractures of the first and second ribs. The tumour had infiltrated the bodies of the sixth and seventh cervical vertebrae. *Brain*: In the floor of the right lateral ventricle a small cellular growth, 2 cm. in diameter, was seen bulging into the anterior horn. The rest of the organs in the body were carefully examined for gross lesions, but there were no pathological findings of significance. *Histological examinations*: (1) Section of the tumour from the lung showed large irregular groups of large atypical polygonal and columnar cells. They are separated by a connective tissue stroma. The cells have very irregular shapes and sizes. The cytoplasm is acidophilic. The nuclei are round and ovoid, and vary in size and shape. Tumour giant cells with multiple round and ovoid hyperchromatic nuclei are seen. There are areas showing a definite acinar arrangement of the cells. The tumour shows areas of marked necrosis and degeneration. The stroma contains a few thin-walled blood capillaries. Tumour emboli are found in blood vessels. *Diagnosis*: Adenocarcinoma grade II (figure 3, plate XX). (2) A section of the brain metastasis showed a histology similar to that of the primary in the lung. (3) A section of the adrenal did not show tumour deposits.

*Summary*.—This patient had a primary carcinoma of the right upper lobe of the lung with a small metastasis in the brain. There was erosion of the first, second and third right ribs and bodies of the sixth and seventh cervical vertebrae. He had pain and wasting of the muscles of the chest and of the right superior extremity. There was myosis of the right eye.

*Conclusion*.—A thoroughly studied case of primary bronchogenic adenocarcinoma of the right upper lobe of the lung with the symptom complex described as Horner's syndrome is reported. There was no evidence to support the idea of a superior pulmonary sulcus tumour being a tumour entity by itself, as originally described by Pancoast.

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## PENICILLIN IN CANCRUM ORIS COMPLICATING KALA-AZAR\*

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CANCNUM ORIS is the most classical and the most fatal complication of kala-azar. Previous to the introduction of the specific treatment with the antimonials, cancrum oris was the terminal event in a large proportion of cases. The incidence of this fatal complication decreased very considerably with the adoption of the specific treatment with the antimonials during the last twenty-five years or so. But during the last three years, particularly during and after the famine of 1943, the senior writer has come across an increasingly large number of cases of kala-azar complicated with cancrum oris; the results of treatment could by no means be regarded as satisfactory, about half the cases admitted to hospital dying.

The treatment adopted was that which had developed during the last 20 to 25 years as a result of treatment of numerous cases in India and abroad. It consisted of: (a) intensive specific treatment with pentavalent antimony compounds, the injections being given daily; (b) general treatment designed (i) to raise the body resistance, viz, adequate nourishment, vitamin intake, blood transfusions, (ii) to combat the infection, viz, sulphonamides (various vaccines and antisera have been abandoned during recent years), intravenous injections of arsenicals in case of Vincent's infections, etc., (iii) to raise the leucocyte count by the injections of pentnucleotide or liver extract; and (c) local treatment generally by mild antiseptics. In some cases sulphonamides were applied locally.

In spite of all these therapeutic measures, the condition was very often fatal. Death was usually due to the spread of infection intracranially, aspiration broncho-pneumonia, obstinate diarrhoea, and asthenia and cachexia due to septic absorption. Sudden death within 12 to 24 hours of admission into the hospital, possibly due to intracranial extension of infection, was also seen. In some cases, the specific and other therapeutic measures did not check the process at all. The worst case the senior writer has seen was in a boy in whom the gangrene spread relentlessly day by day from a small necrosed area in the left cheek to the mandible, left maxilla, left eye, left temporal region, left ear, nose and part of the frontal bone, in spite of the entire regime of treatment

\*The work reported in this paper was undertaken under the Endowment Fund of the Calcutta School of Tropical Medicine, aided by a grant from the Indian Research Fund Association.

enumerated above; ultimately the fatal termination ended the misery of the patient who was conscious almost to the end.

The usual course of the cases that responded to treatment was that for some days the necrotic process kept on spreading to the adjoining tissues; then a line of demarcation formed, and the slough slowly separated leaving a hideous deformity that slowly healed at the margins by granulation. Figures showing the actual proportion of cases that recovered in India are not definitely known. In China where about 15 per cent of kala-azar cases were found to develop cancrum oris, Fu-tang Chu and Chuan Fan (1936) found that 39 out of 79 cases died (about 50 per cent), and in children below 2 years 77.7 per cent cases died.

With the introduction of penicillin and its reported success in the treatment of wound infections about the mouth, it was felt that this drug might prove successful in the treatment of the infective process of cancrum oris. Six cases of cancrum oris coming under treatment between March and September 1945 were treated with penicillin along with the specific anti-kala-azar treatment and general supportive measures. The reports of these six cases are presented below:

**Case 1.**—An Indian child, aged 5 years, was admitted on the 19th March, 1945, for fever, irregular and intermittent in type, for three months, and ulceration of the upper lip and root of the nose for about 1 month. She had been treated outside with some intramuscular injections of antimonials. On admission the child was found to be extremely anæmic and emaciated with a temperature of 102°F.; the spleen was enlarged up to 1½ inches below the tip of the 9th left costal cartilage; the liver was palpable; in the heart and lungs no abnormality was detected. There was a foul-smelling black gangrenous ulceration involving the upper lip, left cheek, root of the nose and a part of the nasal septum (see figure 1, plate XX).

Laboratory findings were as follows: Hb.—4.8 gm. per 100 c.c. of blood; RBC—2,010,000/c.mm.; WBC—5,700/c.mm.; neutrophils—42 per cent; lymphocytes—37.5 per cent; monocytes—19.5 per cent; Türk cells and plasma cells—1 per cent. Antimony test (1:10)—positive; complement-fixation test for kala-azar—doubtful. Stools showed ascaris ova, 1,000/c.c.; pus from the cancrum area showed gram-positive cocci in clusters and chains and fusiform bacilli.

She was put on penicillin and urea stibamine immediately on admission. Penicillin was administered intravenously in 10,000-unit doses every three hours for 6 days, and applied locally in a solution containing 500 units per c.c. for about a fortnight. Urea stibamine was given on consecutive days for ten days and then on alternate days till the 19th injection (total dose 2.3 gm.).

Within 24 hours of the commencement of the treatment, the slough appeared to be getting loose and by 48 hours the slough separated, leaving a clean granulating margin; the foul smell had practically disappeared and the fever had also subsided. The patient progressed steadily except for a slight set-back following an attack of common cold when she required a second course of penicillin in order to check a threatened spread to the nasal septum. The subsequent recovery was uneventful. The patient was discharged on the 16th May with a clean and healed sore (see figure 2, plate XX).

The blood count on discharge was as follows: Hb.—9.07 gm. per cent; RBC—3,650,000/c.mm.; WBC—

5,400/c.mm. She was advised to attend the surgical division of the Medical College Hospital, Calcutta, for a plastic operation.

**Case 2.**—An Indian female child, aged 2½ years, was admitted on the 16th April with a history of fever with chill and rigor for 6 months, attacks of diarrhoea for 3 months and a perforating ulcer of the cheek that had developed during the previous week or so. The child was extremely emaciated and anæmic and had an ulcer covered with slough over the right maxillary antrum. The spleen was enlarged 1 inch below the costal margin and the liver was just palpable. The heart and the lungs did not show any obvious abnormality. The temperature was subnormal.

Laboratory findings were as follows: Hb.—6.18 gm. per cent; RBC—2 million/c.mm.; WBC—74 thousands/c.mm.; neutrophils—46 per cent; lymphocytes—48 per cent; monocytes—6 per cent. The complement-fixation test for kala-azar was positive and tibial puncture showed numerous leishmaniae. Stools—ascaris ova 300/c.cm. and *E. nana* cysts. Urine—no abnormality.

She was put on penicillin 10,000 units intramuscularly every three hours for 8 days, and a solution containing 500 units of penicillin per c.c. was applied locally for about a fortnight. She also had specific treatment for kala-azar with urea stibamine, 0.05 gm. given intravenously for ten consecutive days and then on alternate days in 0.1 gm. doses till a total of 1.5 gm. had been given. By the 25th April she was afebrile, and the ulcer was healing, but there was a fistula opening into the mouth. As the patient was having occasional attacks of fever and the spleen was still enlarged she was given another course of twelve daily injections of aminostiburea, total dose 1.15 gm. She was discharged cured on the 19th June, 1945; she had put on 4 lb. in weight; the spleen was reducible, and the blood count showed some degree of improvement; the ulcer had healed completely leaving a small scar adherent to the maxilla, but the fistula had closed.

**Case 3.**—An Indian male child, aged 3 years, was admitted on the 8th June, 1945, for fever of six months' duration; it was high continuous for about 6 weeks and irregular subsequently. There was a history of occasional swelling of the feet; there was a foul-smelling ulceration over the lower lip and loss of several lower incisor teeth. This condition had developed during the previous seven days.

On admission the patient was found to be very thin and anæmic. He was having a high remittent fever, the temperature rising to 103°F. The hair was thin, dry and lustreless, and the skin showed some degree of pigmentation and dryness. There was a foul-smelling ulceration with black slough involving the lower lip with a fistula into the mouth. Some of the lower incisors were missing and the mandible was apparently affected. The spleen was enlarged (five inches) and the liver was palpable.

Laboratory findings were as follows: Hb.—4.4 gm. per cent; RBC—1.32 millions per c.mm.; WBC—4.1 thousands per c.mm.; neutrophils—52 per cent; lymphocytes—24 per cent; monocytes—20 per cent; plasma cells and Türk cells—4 per cent. The aldehyde test was positive; the complement-fixation test, doubtful. Stools—cysts of *giardia intestinalis*. Culture of swab from the cancrum showed streptococci (not hæmolytic) and *Staphylococcus aureus*.

The treatment with 'stibatin' and penicillin parenterally and locally was commenced from the day of admission. Twelve intramuscular injections of stibatin were given on consecutive days (total dose 90 c.c.). Penicillin was given as in the other two cases. Within 48 hours of the commencement of the treatment, the sore appeared cleaner; the black slough of the lower lip separated, and the foul smell diminished considerably. His general condition also improved, and the fever disappeared from the third day of treatment.

The patient required a second course of stibatin and penicillin because signs of necrosis of the mandible persisted and the clinical evidence after the first course

of treatment did not indicate a cure of kala-azar. He was discharged on the 25th July apparently cured of kala-azar with a healed ulcer on the lower lip. The necrosed bit of the mandible was loose at one end only. He was advised to attend the surgical unit of the Medical College Hospital, Calcutta.

**Case 4.**—An Indian female child, aged 4 years, was admitted on the 9th August, 1945, for intermittent fever with chill and rigor, slight cough, weakness and emaciation for four months. On admission the child was found to be weak, emaciated and anæmic but afebrile. She had cancrum oris involving the whole of the inner aspect of the left cheek. The ulcer was foul smelling and covered with a greenish-yellow slough. A few small whitish patches were also present under the tongue and on the inner aspect of the lower lip. The spleen was enlarged to 2 inches and the liver was 1 inch below the costal margin.

Laboratory findings were as follows: Hb.—6.87 gm. per cent; RBC—2.41 millions per c.mm.; MCV—99.5 $\mu$ ; MCH—28.5 $\gamma$ ; MCHC—28.6 per cent; WBC—3,750 per c.mm.; neutrophils—38 per cent; lymphocytes—48 per cent; monocytes—13 per cent; plasma cells—1 per cent. Aldehyde test—negative. Antimony test—doubtful. Complement-fixation test for kala-azar—negative. Tibial puncture—Leishman-Donovan bodies present. Swab from the cancrum oris—gram-positive cocci and bacilli, gram-negative bacilli, fusiform bacilli, and spirochaetes present. Stools—ova of ascaris, 5,800 per c.c.

The treatment was commenced immediately on admission, with penicillin given locally and by intramuscular injections, and daily injections of stibatin. Within 24 hours of the commencement of the treatment the cancrum appeared cleaner and the foul smell was considerably less. By the next day the smell had disappeared completely. The slough separated on the third day and by the sixth day the necrosis had stopped, and the ulcer was covered by newly-formed epithelial tissue. Her clinical condition had improved considerably and she was discharged as clinically cured of kala-azar on the 3rd September, 1945.

**Case 5.**—An Indian female child, aged 10 years, was admitted on the 27th August, 1945, for intermittent fever with chill and rigor and occasional bleeding from the gums for three months. On admission she was found to be anæmic and emaciated with enlarged cervical glands and œdema of the legs. The spleen was enlarged up to 3 inches and the liver was just palpable. Heart and lungs showed no abnormality. An ulcer was noticed on the left side of the hard palate affecting its anterior half. It was covered with greyish-white slough.

Laboratory findings were as follows: Hb.—6.05 gm.; WBC—2,300 per c.mm. Aldehyde test—doubtful. Complement-fixation test for kala-azar—strongly positive. Sternal puncture—Leishman-Donovan bodies present. Swab from the cancrum—fusiform bacilli, spirochaetes, gram-positive and gram-negative bacilli and cocci.

She was put on daily injections of aminostiburea, penicillin and vitamin C. Within three days the slough separated and the ulcer was free from the foul smell; by the sixth day the ulcer appeared to be healed. Her temperature came down to normal on the fifth day. She was discharged cured a month after admission.

**Case 6.**—An Indian male, aged 22 years, was admitted on the 8th August, 1945, for intermittent fever, occasional attacks of diarrhoea, cough and bleeding from the gums for 3 months, and ulceration inside the mouth for ten days. On admission the patient was found to be extremely emaciated and anæmic, and in a very low condition. He had œdema of the feet and legs, and purpuric spots over the chest; the gums were spongy and bleeding. Three teeth, the upper incisors and the canine, on the right side were missing, and there was a foul-smelling gangrenous ulcer covered with a greyish slough extending over the whole of the right half of the hard palate, and the soft palate showed a large perforation with a sloughing margin.

The inflammatory process extended upwards into the nasal sinuses. The liver and the spleen were just palpable; a hæmic murmur was audible over the heart; no other abnormality was detected.

Laboratory findings were as follows: Hb.—5.2 gm. per cent; RBC—1.6 million per c.mm.; MCV—118.7 $\mu$ ; MCH—32.7 $\gamma$ ; MCHC—27.5 per cent; WBC—2,500/c.mm.; neutrophils—65 per cent; lymphocytes—29 per cent; monocytes—5 per cent; plasma cells—1 per cent. Aldehyde test—negative. Complement-fixation test—strongly positive. Wassermann test—negative. Sternal puncture—Leishman-Donovan bodies ++. Swab from the cancrum—gram-positive cocci, gram-negative bacilli, fusiform bacilli and spirochaetes.

The patient was put on daily injections of aminostiburea, and on penicillin, 20,000 units given intramuscularly every three hours for ten days; penicillin was also applied locally as a spray, and by means of penicillin lozenges kept in contact with the ulcer almost continuously; supportive treatment consisting of glucose intravenously, vitamins B and C and calcium, etc., was given.

By the fourth day from the commencement of the treatment, the foul smell disappeared and the ulcer appeared cleaner. Part of the slough separated, and the margins became more well-defined. His general condition improved to some extent but the anæmia persisted. He was given a blood transfusion of 400 c.c. on the 23rd August, 1945. About three weeks after his admission, the inflammatory process again became active and spread into the orbital cellular tissue of the right side. There was a swelling of the right side of the face and over the eyelids, but there was no rise of temperature. A second course of penicillin was given. The spread of inflammation was checked and an abscess pointed below the right lower eyelid. It was drained by an incision; the pus, on examination of a direct smear, showed gram-positive cocci in clusters and short chains and fusiform bacilli.

At the end of the treatment with penicillin, it was found that the right half of the hard palate was necrosed, and the margins of the perforation of the palate were quite clean, showing granulation tissue. A second blood transfusion was given on the 21st September. On the 28th September it was found that the sequestrum had separated out. Blood tests and clinical features showed that the patient had recovered from kala-azar. The final blood count (3rd October, 1945) was as follows: Hb.—11 gm. per cent; RBC—3,430,000 per c.mm.; WBC—9,800 per c.mm.; neutrophils—72 per cent; lymphocytes—18 per cent; monocytes—7 per cent; eosinophils—3 per cent.

#### Discussion

It will be noted that of the six patients, 5 were children between 2 and 10 years of age and one a young adult, and the duration of illness prior to the development of cancrum oris varied from three to six months. The necrotic process had developed before the patients were admitted into the hospital, and in one case it had developed during a course of specific treatment for kala-azar.

The diagnosis of kala-azar was confirmed by the demonstration of the parasite in four cases. In the other two cases no attempt was made to demonstrate the parasite, the patients being put on specific treatment immediately on admission. In one of these patients who had a small splenic enlargement, the antimony test using the serum dilution of 1:10 was positive; in the other the aldehyde test was positive. The complement-fixation test was positive in three cases only. Though the number of cases is small, it appears that the proportion of positive results

(3 out of 6) is lower in these cases complicated with cancrum oris than in kala-azar cases in general, viz, 93 per cent (Sen Gupta, 1944).

The course of treatment followed in these cases was as follows: (1) Penicillin sodium 10,000 to 20,000 units given intramuscularly or intravenously every three hours for about a week and repeated if required. Local application of penicillin solution containing 500 units per c.c. and as a lozenge in one case, continued for two to three weeks. (2) Specific treatment for kala-azar with pentavalent antimonials, urea stibamine or stibatin, the injections being given daily. (3) General supportive measures, consisting of nourishing diet, vitamins, glucose parenterally, and blood transfusion and hæmatics later if required.

The progress of the necrotic process was found to be quite unlike that seen in the cases that recovered in the previous years. The necrotic process did not continue to extend into the surrounding tissues; in all but one case, the slough separated within 72 hours of the commencement of penicillin therapy; the foul smell distinctly lessened within 48 hours, and was completely absent after 72 hours. The fever commenced coming down after 24 hours and reached normal within the next few days. Apart from the fact that all the patients recovered, the end results of cancrum were fairly satisfactory.

In addition to the above cases, two more kala-azar cases with sloughing of the gum over the third molar and the mucous membrane around it were treated with penicillin, intramuscularly and locally in one, and only locally with penicillin lozenges in the other, with entirely satisfactory results. The yellowish-white slough over the affected areas cleared up readily without extension to the adjoining tissues.

It is not possible to arrive at any statistically sound conclusions about the value of this regime of treatment on the experience of such a small number of cases; but the success that attended this treatment and the marked difference in the course of the necrotic process from that experienced in the past leads the writers to consider that this regime of treatment—penicillin, pentavalent antimonials, and general supportive measures—is likely to meet with better success than the previously adopted method of treatment.

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## A CASE OF MULTIPLE PRIMARY CARCINOMATA

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MACKEE and Cipollaro in their exhaustive monograph 'Cutaneous Cancer and Precancer'

have given a list of causes as precancerous conditions. They say 'many if not most cutaneous cancers develop in a long-standing antecedent, recognizable lesion'. The following case is of interest in that no antecedent lesion can be held responsible for the development of malignant lesions. This patient had several intravenous injections twenty years ago. Even if one assumes these to have been of some arsenical preparation, yet there was no sign of arsenical dermatitis or keratosis, and the malignant lesions were far removed from the palms and soles. While discussing senile keratosis they say 'recent experiments on albino animals have shown that long-continued exposure to sunlight or ultra-violet light may incite cancer, but animals with dark hair do not develop cancer from exposure.' This patient was an albino.

#### The case

Mr. V. L., aged 62 years, came to the hospital on 6th June, 1943, with a complaint of (1) two raw bleeding swellings, one in the left fronto-temporal region and one in the deltoid region of the left arm, and (2) two ulcers, one on the left side of the nose and one involving the right ear.

*History.*—About eight years ago the patient noticed two swellings, one on the left arm and one in the left occipital region. Both the swellings were removed by operation. The wounds however took a long time to heal. Since then for nearly six years he had had no trouble of any kind when about 2½ years ago he developed an ulcer on the lobule of the right ear. The ulcer persisted for a long time until the medial half of the lobule was eroded. The ulcer then healed in that region, leaving a clean postero-lateral half of the lobule. But the ulcer then appeared in front of the tragus of the same, i.e. the right ear, and on the inner aspect of the auricle. About 18 months ago he noticed the two above-mentioned swellings—those on the fronto-temporal region and on the arm. He cannot say exactly when the ulcer on the left side of the nose first appeared.

The patient and one of the two brothers are albinos, while the third brother and one sister have normal complexions. No other member of the family is an albino. The patient had taken several intravenous injections about 20 years ago. He does not know the name of the injections and would not tell the reason why he took those injections.

*Findings.*—W.R. and Kahn tests are negative. The urine does not show any abnormal constituents.

1. Arm swelling: A cauliflower-like fungating slightly flattened swelling about 3 inches in diameter is situated in the region of the deltoid muscle on the lateral aspect of the left arm. The tumour has a pedicle about 2 inches in diameter, and it appears as if this pedicle is growing out of an opening in the skin. The growth has a hard edge, and the whole growth is nodular on the surface. It is not attached to the deeper tissues, for on contracting the deltoid muscle the tumour can be moved about quite freely. The tumour is situated just below the scar of the previous operations. In this operation scar about 1 inch below the tip of the acromion can be felt a small hard nodular mass about ½ inch × ½ inch. This mass is completely covered with the scar to which it is adherent. On contracting the deltoid muscle, the mass becomes slightly anchored.

2. The fronto-temporal tumour. This tumour is raw and fleshy-looking, but almost smooth on the surface, and bleeds easily on touching. It is about



Fig. 1.—X-ray plate showing an opacity in the region of the right upper lobe of the lung.



Fig. 2.—Photograph of the cut surface of the tumour of the lung.

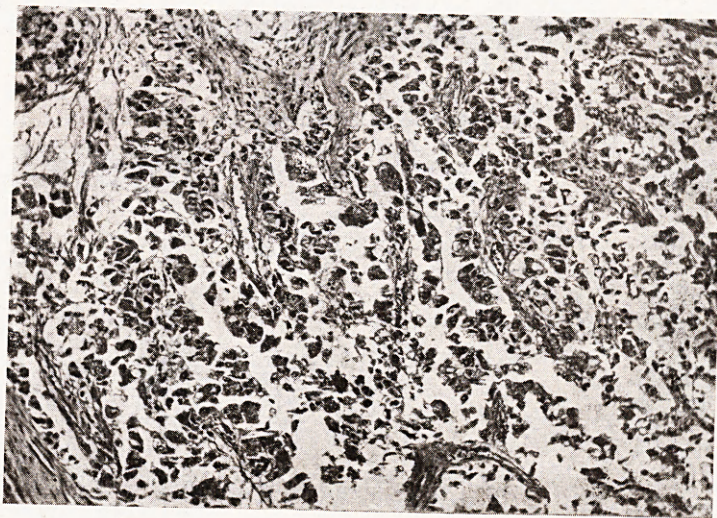


Fig. 3.—A low power photomicrograph showing a structure of an adenocarcinoma.

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Fig. 1.—Case 1. Extensive cancrum involving cheek, lip, root of nose and nasal septum.



Fig. 2.—Case 1. After treatment.