COMPLICATIONS OF CANDIDA ALBICANS INFECTION IN INFANCY

BY

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Thrush was first described in 1764 by Rosén von Rosenstein, who mentions a disease of the mouth, more severe if it spreads into the lungs. Thrush infections were later described by Langenbeck in 1839, Berg (1841), and Robin (1853). Robin called the organism *Oidium albicans*, and in 1890 Zopf renamed it *Monilia albicans*. From then until the present time the organism, now known as *Candida albicans*, has been adjudged to be responsible for disease in man. During recent years, since the discovery of broad-spectrum antibiotics, increased interest has been paid to the severe effects which may be produced. In infancy, thrush has long been known as a common disease occurring especially in sickly and undersized children. The majority of cases present an oral disease of varying severity, but many reports have been written of far more serious consequences of invasion by the fungus. These usually involve local spread to the gastro-intestinal or respiratory systems, but monilial septicaemia with metastatic disease is also described.

The purpose of this paper is to present four cases of thrush oesophagitis and to review previous writings on the complications and treatment of *Candida albicans* infections. Three of the cases present a very definite syndrome which is due to thrush, though the oesophagitis cannot be proved with certainty, and the fourth is a fatal case of thrush oesophagitis proved at necropsy.

Case 1

A male infant aged 26 days was admitted to hospital on November 10, 1956, with a history of cyanotic attacks and difficult breathing for five days. He had a full-term normal delivery but difficulty in sucking from birth. On the day of admission severe thrush was noted.

On admission he was a well-nourished infant weighing 7 lb. 2 oz. (3.2 kg.). He was very dyspnoeic (rate 60 a minute), was cyanosed, and had marked stridor and intercostal recession. His temperature was 98.4° F. (36.9° C.). There were rhonchi throughout both lung fields. He had a grade III systolic murmur in the fourth left interspace suggestive of a ventricular septal defect, but no signs of congestive cardiac failure.

He was nursed in an oxygen tent moistened with "alevaire" and given penicillin, 250,000 units six-hourly, streptomycin, 75 mg. twice daily, nystatin, 100,000 units six-hourly, and 0.5 ml. injections of vitamin B complex on alternate days. He was offered feeds of expressed breast milk.

X-ray examination of the chest (Fig. 1) revealed bilateral bronchopneumonia. A blood count showed a haemoglobin of 15.3 g. per 100 ml. and 11,700 white cells (polymorphs 47.5%, monocytes 0.5%, lymphocytes 51%, eosinophils 1%). An oral swab grew candida.

For a few days the child improved generally, though the thrush remained obvious. He then deteriorated rapidly, was cyanosed outside the oxygen tent, and had very pronounced blue attacks, mainly during feeding.

A "lipiodol"-swallow examination on November 21 (Fig. 2) showed pooling of the oil in the pharynx with spill-over into the lungs. An aspiration pneumonia affected the major

portion of the right lung and the mid-portion of the left. It was then decided to take him off all oral feeds and medicines and to give him an intravenous drip. This treatment was continued for 10 days—the fluid containing appropriate electrolytes and vitamins, and plasma was given daily. His condition improved, his colour became pink, and all chest signs disappeared. On one occasion—three days after this treatment was started—he was fed and became extremely cyanosed. On November 30 a repeat lipiodol swallow (Fig. 3) showed easy passage from pharynx to oesophagus with no spill-over. The lung fields had almost cleared.

From December 1 slow oral feeding was resumed and he made an uninterrupted recovery (Fig. 4).

Case 2

A male infant aged 15 days was admitted to hospital on March 17, 1956. He had been quite well until he was 8 days old, when he developed thrush. This became worse in spite of treatment, and for a few days before admission he had been breathless and had vomited some of his feeds.

FIG. 1.—Case 1. Chest radiograph before treatment.

FIG. 2.—Case 1. Radiograph of lipiodol swallow before treatment.

On examination he was afebrile but extremely ill, cyanosed, and dyspnoeic, and frothy mucus was bubbling from his mouth. His mouth was swollen and showed severe thrush with some ulceration. Chest examination revealed recession, and on auscultation rales and rhonchi were heard throughout both lung fields. On attempting to swallow he became very blue and regurgitated most of what was taken. A lipiodol-swallow examination showed a spill-over into the trachea and that some of the oil would not enter the stomach through the cardiac sphincter. This was thought to be due to reflex cardiospasm due to oesophagitis. Treatment was instituted immediately; oral feeding was entirely stopped and intravenous drip, penicillin, streptomycin, and nystatin (100,000 units, four-hourly) were given.

Two days later the child was a little better but still extremely ill, and hydroxystilbamidine, 10 mg. intravenously daily, was started. On March 24 oral feeding was again

tried, but there was immediate deterioration. X-ray examination at this stage (Fig. 5) showed a right basal pneumonia. Intravenous therapy was again started, though small oral feeds were continued. The condition improved very gradually. On April 8 lipiodol-swallow examination was repeated, and on this occasion the oil passed rapidly from mouth to stomach without spill-over or hold-up.

The patient was discharged well on May 5.

Case 3

A female patient aged 5 weeks was admitted to hospital on January 7, 1954. She had a normal history until 3 weeks of age, when she developed thrush of the mouth, which was treated daily with 1% gentian violet without improvement, and then unsuccessfully with chlortetracycline. She had been very difficult about taking feeds throughout this period. For one day she had had a cough.

On admission her temperature was 101° F. (38.3° C.), but she appeared to be fairly well. She was not cyanosed or dyspnoeic, but she dribbled continually from her mouth. Her chest was clinically quite clear. There was very marked thrush of the mouth. She was treated with penicillin, "bejectal," and local gentian violet. Two days later the mouth was worse and local chlortetracycline was tried. The mouth remained unhealthy, and on January 15 signs of severe pneumonia were present clinically and were con-

FIG. 3.—Case 1. Chest radiograph after treatment.

FIG. 4.—Case 1. Radiograph of lipiodol swallow after treatment.

FIG. 5.—Case 2. Radiograph taken during treatment.

firmed by x-ray examination (Fig. 6). The plates were reported as being unlike moniliae of the lungs. Following this, her condition deteriorated rapidly in spite of oxytetracycline and chloramphenicol. It was noted that feeding caused marked distress and cyanosis. She died on April 22. Unfortunately necropsy was refused.

Case 4

A male infant aged 9 months was admitted to hospital on April 21, 1952. His history was of a normal child until four days before admission, when he developed vomiting and an acute diarrhoea. These symptoms were not improving, so he was brought to hospital. On examination his temperature was 102° F. (38.9° C.); he was dehydrated and showed signs of malnutrition. His weight was 12½ lb. (5.7 kg.). Other positive signs found were severe thrush of the

mouth and pharynx and rhonchi throughout the lungs. Both the liver and the spleen were just palpable.

He was given intravenous fluids, intramuscular penicillin and streptomycin, and gentian violet was used locally. Oral feeding of skimmed milk and water was begun after 24 hours. Initially he improved on treatment, but the thrush never cleared. On April 30 he was noticed to be jaundiced, rather chesty, and cyanosed, and his chest was full of rales. His temperature rose to 103° F. (39.4° C.). After this his condition rapidly worsened, and he died two days later.

Necropsy showed a dehydrated child, with marked thrush of mouth and pharynx. The lungs showed basal congestion. The oesophagus was thickened and the surface covered with thick white granular membrane which stopped short at the entrance to the stomach. Histology of the oesophagus showed acute inflammatory changes with exudation and superficial necrosis, and on Gram's stain the presence of *C. albicans*.

FIG. 6.—Case 3. Radiograph of chest.

Aetiology and Frequency of Moniliasis

C. albicans may be found in the normal mouth flora, especially in older children and adults. In the newborn and infants, where the oral pH is high, it is usually introduced from the exterior and causes disease. There is an increased incidence in children of mothers suffering from vaginal moniliasis. This has been observed many times, and one experiment was done to prove that vaginal thrush could be introduced into the mouth of the newborn, producing disease (Hesseltine *et al.*, 1934). Some nurseries have reported an incidence of infection as high as 18.2%. Apart from vaginal thrush as a cause, many cases must be produced by direct spread due to nurses' fingers, bottle teats, dummies, etc. Any trauma to the oral mucosa will increase the likelihood of infection. Airborne infection seems to play no part in the spread.

In any age group the use of broad-spectrum antibiotics has increased the incidence of moniliasis.

Complications of Moniliasis

Oral thrush, which in itself can be a severe disease interfering seriously with nutrition, can spread to cause three types of disease: (1) spread into the gastro-intestinal tract, especially the oesophagus; (2) spread into the lungs; and (3) systemic spread.

Gastro-intestinal Spread

As gastro-intestinal spread is the main topic of this paper it is dealt with in more detail than the other complications, especially as regards oesophagitis. The diagnosis of oesophagitis in Cases 1-3 cannot be proved. However, the syndrome which they represent is a definite one whether it be due to actual spread to the oesophagus, as some authorities have felt, or to an incoordination of swallowing due to thrush of the posterior pharynx, either leading to inhalation of food and aspiration bronchopneumonia. This syndrome may be described as one in which a baby with oral thrush becomes very toxic and sometimes dehydrated, has difficulty in swallowing, and during feeds is noted to choke and become cyanosed. Within a short period a severe bronchopneumonia develops, and without active treatment death may easily follow, as happened in Case 3. To substantiate the diagnosis x-ray films of the chest will show marked bronchopneumonia, and lipiodol swallow an incoordination of swallowing either at the upper (Case 1) or at the lower (Case 2) end of the oesophagus. Culture of the oral flora can show that *C. albicans* is present, but not at what level of the gastro-intestinal tract. Some authors working on adults with similar clinical pictures have performed oesophagoscopies on their cases, and shown that the oesophagus is involved in a disease similar to that in the mouth (Stenderup *et al.*, 1956). Such an investigation was not thought safe in these very ill babies.

In the literature this syndrome is well described. Ebbs (1938) performed necropsies on 28 infants under 10 months of age, the average being 4 months, all of whom had died of oesophagitis: 22 had thrush oesophagitis. The clinical picture in these children was very similar to that described above. Reye (1941) found that of 150 necropsies 10 showed oesophagitis, which was the cause of death in seven and in five was due to thrush. Henderson (1943) reviewed 163 cases of thrush during a three-year period, and 13 of these had oesophagitis and seven died from its effects. Adams (1944) described five fatal cases of thrush pneumonia in infants with a similar clinical picture. Lederer and Todd (1949) did routine necropsies on 28 infants under 4 weeks and on 176 under 1 year of age. In seven of the former and 19 of the latter moniliasis was thought to have caused death. Clinically a syndrome of vomiting and dehydration with aspiration of vomit and septicaemia is described. Six patients died suddenly from blocking of the respiratory passages.

Wolff *et al.* (1955) describe two cases identical with our Cases 1-3. Both responded well to similar treatment. Andrén and Theander (1956) and Geiger *et al.* (1946), writing on two adults, mention typical x-ray changes of oesophageal moniliasis. Both had been on long courses of antibiotics and were x-rayed because they had oral thrush with dysphagia. The entire thoracic oesophagus was irregular and ragged, and was made up of numerous small indentations and protrusions. Longitudinal folds were discernible and the lumen became distended on passage of a large bolus. Stenderup *et al.* (1956) had three adult patients with thrush, and in two oesophagoscopies showed thick coating of the oesophagus with monilia-like lesions.

Two authors mention intestinal moniliasis. MacGregor and Henderson (1943) examined two children found dead at home in whom marked intestinal thrush was present, and Zimmerman (1950) quotes a personal communication from Dr. Sydney Farber of five cases of disseminated moniliasis in childhood in which the primary site was the oesophagus or the intestines.

Thrush oesophagitis is a reasonably common disease, and, though for many years it was thought to be diagnosable only at necropsy, there is no doubt that it can be diagnosed and treated during life.

Broncho-pulmonary Moniliasis

Much controversy has arisen whether primary moniliasis of the lungs exists or not. From the first mention of the

condition by Castellani in 1905 until now, many authors have published reports of cases. Many, however, feel that there is no such disease and that where moniliasis is found in the lungs it is a secondary infection. Actual proof of moniliasis is made difficult by two factors—that it is hard to prove that a positive candida culture comes from the lungs when oral moniliasis is present, and that after death moniliasis is a common secondary infection of tissues. There is no doubt, however, that at any age oral thrush can be complicated by pneumonia, which is not always due to inhalation. Some cases—for example, that described by Beckmann *et al.* (1955) with prompt response to nystatin, and the fatal case described by Falkmer and Wising (1955)—are very convincing cases of primary broncho-pulmonary thrush. Sahni (1957) describes a case without primary lung disease in which the patient responded adequately to treatment with potassium iodide and nystatin. It seems that pulmonary moniliasis must be regarded as a serious complication of the oral disease.

Systemic Moniliasis

A number of cases have been described of septicaemic spread of candida infection, with widespread lesions developing. References to the following cases were found:

Two patients with monilia meningitis, one of whom was found to be quite well after a four-year follow-up (Fine *et al.*, 1955; Carnu and Charanis, 1954).

A patient who died of thrush and was found at necropsy to have a perinephric abscess, thrombosis of the inferior vena cava, and bronchopneumonia, all growing pure *C. albicans* (Brown *et al.*, 1953).

A patient who at necropsy had multiple abscess of the brain, myocardium, and kidneys due to monilia (Brown *et al.*, 1953).

Two further cases quoted by Brown *et al.* were found at necropsy to have monilial abscesses of myocardium, kidneys, and lungs. Blood culture grew *C. albicans* in one case and *C. tropicalis* in the other. Both cases had had long courses of broad-spectrum antibiotics.

Zimmerman (1950) quotes the case of a patient who died of mycotic endocarditis, and mentions a personal communication from Dr. Sydney Farber quoting five cases of disseminated moniliasis in children being treated with various chemotherapeutics, and at necropsy there were widespread fungus lesions. The primary site in all was the oesophagus or intestines.

Geiger *et al.* (1946) quote another fatal case of *C. albicans* endocarditis.

Although these are not a vast number of cases, they do present a frightening aspect of the possible outcome of thrush.

Pathology

Case 4 illustrates the pathology of thrush oesophagitis. The organism grows as patches of greyish-white membrane on the mucous surfaces, this membrane consisting of a tangled growth of Gram-positive hyphae with spores produced at the junctions of the segments. Permeation and destruction of the epithelium occur and often there is secondary bacterial growth. The oesophagus is either primarily involved or involved through secondary extrusion from a contiguous lesion. There may be either superficial erosion or actual pseudomembrane formation with mycelial threads found in the tissue sections.

Treatment of Moniliasis

In the majority of simple cases of not very ill children with oral thrush local measures will suffice. These consist of gentle handling so as not to traumatize the mucosa, and swabbing with at most three daily applications of 1% gentian violet solution. If this is ineffective, and in more severe cases, drug therapy should be started. The possibilities in this direction are:

Nystatin, an antifungal agent derived from cultures of *Streptomyces noursei*, in doses varying from 50,000 units four times daily in the newborn to 500,000 units in adults, has proved a very powerful antimonilial weapon. It has eliminated or reduced

the number of candida organisms in the stools of 25 adult patients in 48 to 72 hours (Sternberg *et al.*, 1953-4). It is poorly absorbed from the gastro-intestinal tract and is mainly of use locally. There are few or no toxic effects.

Hydroxystilbamidine, which is one of the aromatic diamidine compounds and has been used in various mycotic infections, was found useful by Wolff *et al.* (1955) in two cases of thrush oesophagitis. The dosage suggested is 5 mg. per kg. given 12-hourly for four to six days. Toxic effects, such as trigeminal neuralgia and renal damage, which are common with stilbamidine therapy, have not been reported. There is a marked tendency to thrombophlebitis of the veins used for the intravenous injection, and there are reports of weakness and even circulatory collapse following the injection. In a series of three cases in adults pentamidine was found very effective (Sutcliffe *et al.*, 1954).

Brilliant green has been successfully used locally, intravenously, and by aerosol in cases of pneumonia. The suggested dosage for intravenous use is 0.16 to 0.5 mg. per kg. daily, and by aerosol 2 ml. of 0.1 to 0.2% solution in 50% propylene glycol by oxygen inhalation.

Potassium iodide has been effectively used in many cases, but largely in conjunction with other drugs.

"Paraben" (parahydroxybenzoic acid) has been used experimentally in moniliasis caused by chlortetracycline and found to be effective. So far it has not been found useful therapeutically, but it may be in the future. It is a substance used to prevent fungus growth in foods.

Recently other chemotherapy has been successful in some cases. (a) 1,2,3,4-Tetrahydrofluorenol (T.H.F.) was tried with excellent results in a child with lung thrush following a skin infection (Lindquist, 1957). He reports a series of 30 cases treated by A. Frisk with favourable results in 50%. (b) 2,2-Dihydroxy-5,5-dichlorodiphenylsulphide has been used systemically with success in one case. It was previously used only locally (Richter, 1950). (c) Sodium caprylate has been used in two cases (Keeney, 1946).

Additional and supportive therapy varies according to the complication present. Difficulties of feeding are obvious in cases of oral thrush, as is the need for oxygen in pneumonia. The vital stopping of all oral feeding in cases such as those described here must be borne in mind and instituted before fatal inhalation pneumonia occurs. Intravenous therapy must be continued until a lipiodol-swallow examination shows the baby is able to swallow properly.

Summary and Conclusion

Four cases of thrush oesophagitis are described; two patients survived and two died. An attempt is made to describe the clinical syndrome related to this complication of thrush and how it should be treated. There is a review of cases described with one or more of the complications of oral thrush and their outcome. The possible therapy and the pathology of the condition are outlined.

Whilst oral thrush is an extremely common condition in newborn and infants' wards, the severer complications are not so well known, and as therapy may be life-saving, especially in cases of oesophageal spread, an attempt is made to review some of these complications. Thrush oesophagitis, or a syndrome as cited to it, is fairly common, and often fatal if unrecognized or incorrectly treated. The entity of monilia bronchopneumonia definitely exists, whether as a primary or a secondary disease. Rarer complications, especially monilial septicaemia, are worth remembering, though they are mainly diagnosed at necropsy.

One feels that no case of oral thrush should be regarded light-heartedly until all traces of the disease have cleared up and one is certain no complications have developed.

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AMIPHENAZOLE AND MORPHINE IN PRODUCTION OF ANALGESIA

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Shaw and Bentley (1952) were the first to point out that a dog completely narcotized with morphine (and sometimes hyoscine) could be restored to normal within a few minutes by an intravenous injection of 2:4-diamino-5-phenylthiazole (amiphenazole; "daptazole," DHA 245). The most interesting part of this phenomenon was the complete restoration of consciousness of the dog. This work has been confirmed (Gershon and Shaw, 1958). It was also shown that the analgesia produced by the morphine was not affected by the amiphenazole.

By means of the use of amiphenazole, large doses of morphine (up to 200 mg. q.i.d.) were given to patients suffering from intractable pain in terminal carcinoma (Shaw and Shulman, 1955; McKeogh and Shaw, 1956).

This use of the combination of morphine and amiphenazole has continued in Melbourne for a period of nearly four years. The same excellent results have been obtained in about 500 patients. The combined drugs have been used by others in a similar manner (Hügin, 1956; Holmes, 1956; Hayward-Butt, 1957; Dundee, 1957; Overton, 1957).

These early results led us to believe that amiphenazole was a morphine antagonist similar in nature to nalorphine, etc., with the exception that the analgesia was not antagonized and that amiphenazole had no side-effects when given alone. Recent work by us (Christie *et al.*, 1958) has led us to modify this view.

It is the purpose of this paper to explain the exact nature of the action of amiphenazole. In a previous paper (Christie *et al.*, 1958) we had shown that amiphenazole had little influence on morphine-induced nausea and vomiting. Cyclizine chloride ("marzine") is the drug of choice here. Amiphenazole has an irregular stimulating action on an already established morphine-induced respiratory depression when given as a single dose. Although Shulman and Trethewie (1956) refer to amiphenazole as a respiratory stimulant, others have noted its unsatisfactory respiratory stimulant action, and on this account have dismissed the drug as being valueless as a morphine antagonist (Bonnycastle and Costa, 1955).

Our approach to the problem has been to obtain objective evidence that amiphenazole does influence the action of morphine. The main approach has been through psychological testing. Unfortunately, the material at our disposal, elderly and failing cancer patients, has not remained in a constant state long enough to enable adequate controls to be used. The difficulty of carrying out such work on healthy volunteers has been stressed earlier (Christie *et al.*, 1958). Although the psychological testing has been of help to us, we have had to rely more on the observations of trained personnel, nursing and medical, and especially the medical specialists in charge of the cases. We would be the first to admit the inadequacy of such evidence, but we are impressed with the unanimity of opinion expressed despite staff changes which occurred over a period of four years. One of the members of the present team is an experienced psychologist.

In all, 27 cases have been assessed for the work. Below are given case histories of 10 patients whose condition and responses permitted the nearest approach to a controlled experiment. The remaining 17 cases showed aspects similar to these, but the results were neither so clear nor so extensive.

Material and Methods

The series consisted of 27 patients with intractable pain of terminal carcinoma. The sexes were about equally represented. No attempt was made to classify the type of malignancy. Similarly, the assessment of pain was on a subjective basis. While this method may be open to objections, nevertheless it was felt that the duration and extent of the pain made the results more reliable than they would be, for instance, in post-operative pain.

Psychological Testing.—As has been mentioned, two major obstacles are encountered in obtaining measures of the behavioural changes which are indicated by clinical observation: (a) patient impaired by illness, and (b) lack of tests known to be sensitive to these changes. Several techniques were attempted, however, and these have provided indications that the effects are measurable and may be better