fat from the back of the duodeno-jejunal junction, a few tiny glands being included therein. The pathological report reads: "Adenocarcinoma of jejunum, with mucoid change in the deeper portions. Penetration of the bowel is complete. A small lymph gland shows no secondary invasion."

Convalescence was satisfactory, and he remains well.

Case 4

A bus-driver aged 35 had been in hospital a year previously under Professor Melville Arnott with thrombophlebitis migrans, which led to thrombosis of the superior and inferior vena cava; no satisfactory explanation had been found for this.

On April 11, 1952, he was readmitted under Professor Arnott, this time as an emergency case. He said that since his previous spell in hospital he had been perfectly well until a month previously, when he began to suffer epigastric pain, which went through to the back and was colicky in nature. It was unrelated to meals, and was relieved by heat and "veganin" tablets. Alkalis were ineffective. He began to vomit four days before, at first in small quantities, but then in larger amounts. The vomit was yellow, and on admission occurred every half-hour. On the day of admission the vomit was darker brown, and contained a little blood. With the onset of vomiting the pain became easier. The bowels had acted regularly each day, including the morning of admission.

The patient did not think he had lost any weight, though his appetite had become poor. He regarded himself as cured from the former thrombosis trouble, having been at full work since then, and had not noticed any swelling of arms, legs, or face. However, he became breathless on exertion and admitted to some swelling of the face after walking more than 200 yards.

On examination he was thick-set and looked ill, flushed, and anxious, and he vomited coffee-ground material frequently during the interview. Temperature 99.8° F. (37.7° C.) and pulse 80. Micturition and urine were normal. In the epigastrium was a tender rounded mass transmitting pulsation. The liver was enlarged to three fingerbreadths below the costal margin. Neither spleen nor kidneys were palpable, and no abnormality in the pelvis was found on rectal examination. The axillary glands were enlarged. The neck veins were full, but no other abnormality of cardiovascular or respiratory systems could be found. The testicles were normal.

At this stage I was asked to see this man, and did not feel I could be more precise than to say that he had high intestinal obstruction and required laparotomy; but I remarked to one of my team that the case reminded me of the three cases described above.

Operation (April 13).—The abdomen was opened through a left paramedian incision. The lump previously felt on examination was found to be a retroperitoneal mass, which on closer examination proved to be part of a gross generalized intra-abdominal adenopathy. The glands along the aorta and both iliac arteries were enlarged and fused together, as also were those in the mesentery, mesocolon, and mesosigmoid, and there was a further mass in the hollow of the sacrum to which the rectum was tethered. In the region of the main mass—namely, behind the stomach and duodeno-jejunal junction—the peritoneum was puckered, giving the appearance of being infiltrated by growth, and the transverse mesocolon was so shortened thereby that the colon was drawn right back on to it. In the same way the duodeno-jejunal junction was affected, but, so far as could be detected, there was no involvement of the stomach wall itself. The effect of this adenopathy was therefore to narrow the duodeno-jejunal junction considerably. An anterior gastro-jejunostomy was performed as a short-circuiting device. No secondary deposits could be felt in liver or spleen. A gland from the mesentery was removed for biopsy. The patient made an uninterrupted recovery.

The report on the mesenteric gland was that there was no evidence of neoplasia, but marked inflammatory hyperplasia with sinusoids distended with reticulum cells. Because of this somewhat unsatisfactory explanation of his illness, glands were removed from each axilla, but precisely the same appearance was reported.

He was discharged home on May 14 in excellent condition, and has since remained so.

Conclusions

The outstanding features of these four cases are: (1) a short history—a matter of weeks only—of epigastric discomfort or pain; (2) the onset of vomiting very shortly afterwards; (3) the vomits contained bile in all four cases; (4) in all four the symptoms were those of high small-intestine obstruction of a subacute nature.

The short history and fairly sharp onset were against pyloric stenosis from ulcer or neoplasm, and so, too, was the presence of bile in the vomits and the fractional test meal. The absence of collapse from severe colic was against acute obstruction of the small intestine, but the copious and oft-repeated vomiting, together with dehydration, pointed to partial obstruction at a very high level. That several mechanisms may lead to such partial obstruction is shown by these four cases.

THE MANAGEMENT OF CHILDREN WITH PRIMARY TUBERCULOSIS*

BY

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To guide a patient satisfactorily through any illness we must be thoroughly familiar with the natural history of the disease and the possible variations of its course, particularly those dependent on the age and circumstances of the patient. In this paper we deal with the child who has his first infection with tuberculosis—that is, with a primary tuberculous focus and the accompanying tuberculous adenitis of the regional lymph nodes.

What advice should be given concerning the child with the primary tuberculous infection? How does the advice accord with the stage of the infection, the age of the child, and the circumstances in which he lives? These are the practical questions of medical practice, and to answer them we must know the natural history of the disease. It must be confessed that in spite of the vast expense and labour involved in the study of this disease process there are great gaps in our knowledge. Many of the fundamental features of the natural history of the primary and post-primary infections are still unknown.

Natural History of Primary Tuberculosis

Nine out of every ten of our population undergo a primary infection with tuberculosis before the age of 20. The entry of the tubercle bacillus into the lungs

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with the formation of a primary focus takes place, in 80-90% of those infected, after contact with an infective adult. In the remainder, it occurs in the abdomen, in the nasopharynx, or on the skin. Wherever the site of the initial infection, whether it be visible as in the skin or invisible as in the lungs, a small tuberculous lesion appears, and the neighbouring lymph nodes enlarge.

The primary complex often forms without any disturbance of general health, and usually both the focus and the glands are painless. In an unknown proportion of children there is, however, about two to four weeks after infection, a general febrile reaction, with malaise and sometimes joint or muscle-aching, but without other abnormal clinical signs unless sensitivity reactions such as erythema nodosum or phlyctenular conjunctivitis occur. If the regional glands are visible in the neck or axilla or groin, as they may be from about 14 days after infection from a neighbouring primary infection, they may become tender and may indeed simulate an acute pyococcal infection. If in the abdomen, they may form a palpable mass and give rise to pain. Whether or not there is a febrile reaction, the body becomes sensitive to tuberculo-protein about four to six weeks after infection, and this altered sensitivity is turned to diagnostic or epidemiological use in the various tuberculin tests.

This febrile reaction, or "fever of onset," settles within a month; if it be prolonged thereafter we should suspect either extension of the primary focus or the beginning of disseminated disease. For the real immediate danger of the primary infection is that in a small proportion of cases, varying with age, with inborn resistance, possibly with nutrition and intercurrent infection, widespread dissemination of the tubercle bacilli will give rise to miliary tuberculosis or tuberculous meningitis. In others, again an unknown proportion of those infected, though widespread and overwhelming infection does not ensue, localized complications occur: in the lung there may be bronchial erosion or occlusion, or pleural effusion; in the body, lesions in bones or joints. These complications, widespread and local, are most likely to arise in the first two years after infection, the risk diminishing afterwards. Fortunately, though we do not know the proportion of children who develop other tuberculous lesions after primary infection, we can say that in the majority the primary complex is healed and either disappears or is calcified. Once this has taken place the child seems to enjoy a period of relative safety from tuberculosis until young adult life brings the risk of localized chest lesions of "bronchogenic" or "adult" type—lesions arising either by reactivation of bacilli derived from those causing the primary infection or by new bacilli introduced from outside.

In this outline of the natural history of the primary infection there are certain important gaps. We know that dissemination is most likely to occur in children infected in the first two years of life, but we do not know the risk of dissemination at different ages and under different conditions; we do not know which individuals are likely to develop miliary tuberculosis or meningitis.

We know that we shall be asked for advice under two very different conditions. First, there is the child who is clinically ill; secondly, there is the child with a primary complex in the chest discovered in a routine examination at school, as a tuberculous contact, or in the course of investigation for some other condition. These two groups of children present quite separate problems.

Asymptomatic Primary Pulmonary Tuberculosis

When such a child is found what do we recommend? Should we advise treatment at home, or in hospital? Is active treatment necessary, or should we wait and see? Our attitude to these questions must depend upon our estimate of the chance of the development of clinical illness and, more particularly, of dissemination. We therefore need to make a numerical estimate of the risk of dissemination. Such an estimate is only possible for a given population when the conditions for study are favourable. But they are so fundamental that I wish to give the estimate which Dr. Cammock and I have recently made for children infected under 5 years of age in Newcastle-upon-Tyne.

The study in which this estimation was made is still in progress, but, very briefly, we have been able to trace the tuberculous history of all the children under 5 years of age in Newcastle on December 31, 1949. We have been able to estimate that 1,200 of the 25,000 children under the age of 5 would have undergone or be undergoing primary infection—ranging from 2% of those under 2 years to 10% of those in the fifth year of life. In Newcastle, such ill children reach hospital, and we have had help from the staff and access to records of all children's units.

From January, 1945, to December, 1951, 41 of the 25,000 children who would still have been under the age of 5 in December, 1949, developed tuberculous meningitis or miliary tuberculosis, or both. The risk of a child developing tuberculous meningitis or miliary tuberculosis is therefore about 1 in 30, or 3%. This is almost certainly the period of greatest risk. Over this age, during the school years, the chances are probably less, but as a matter of urgency we need to know the risk of primary infection in both school years and adolescence.

The next question we ask is, Knowing the risk of dissemination in untreated cases, can we design an experiment to prove that treatment will alter the likelihood of dissemination? With a risk of 3% and a treatment 100% effective we would need at least 300 children under the age of 5 years with a known recent primary infection before the result would be likely to be statistically significant; with a remedy 50% effective the group would have to be doubled. It seems, therefore, very unlikely that the conditions for such an experiment could be realized. Thus we have not as yet, and for a long time to come we will probably not have, the data to determine the results of treatment of the asymptomatic primary tuberculous complex.

At the present time, therefore, with the possible exception of the very young infant, I do not recommend chemotherapy for the well child who has a pulmonary primary infection. Nor do I, except where the child's home is quite inadequate to provide proper care and attention, advise hospital or sanatorium treatment, for I believe it is particularly desirable to keep young pre-school children at home, or at least in a family where they can feel secure.

Is there, then, anything we can do for the child who has recently undergone infection but remains well? I believe—a great deal can be done. We can see that he receives adequate food and sleep and otherwise lives a normal life, even to attending school. Intercurrent infections must be promptly treated, but above all we must always be alert for the insidious changes which denote *early* tuberculous meningitis or miliary tuberculosis. Prognosis now in these conditions depends more than anything else upon the length of time between onset and diagnosis. Diagnosis depends upon the early recognition of change of habit or health in a previously well but infected child. Vomiting without obvious cause repeated for more than two or three days, refusal of food, and irritability are signs to look for; in the older child headache should raise our suspicions, or in the case of miliary tuberculosis an unexplained pyrexia or loss of weight. The complications will be diagnosed from the history (often a history of contact with adult infection can be obtained), and from knowledge of previous tuberculin conversion, confirmation will be obtained by

lumbar puncture or radiology. For the family doctor, however, the key to the situation is the use of the tuberculin test in the children in his practice.

Treatment of Children Ill with Pulmonary Primary Tuberculosis

In the treatment of children ill at the time of primary infection, or with local complications later, advice is required on the necessity for rest, whether that rest should be at home or in hospital, and whether streptomycin and *para*-aminosalicylic acid (P.A.S.) should be used.

The commonest clinical manifestations of the primary complex are the initial fever with malaise, and limb and joint pains simulating and often mistaken for rheumatism; the child loses appetite and weight, and sometimes the skin becomes peculiarly dry and coarse. The spleen may be felt, though it is seldom greatly enlarged. After confirmation of the diagnosis and the taking of radiographs the child may be kept at home in bed if the home conditions are adequate. The fever of onset does not usually last longer than a month, and, provided a close watch is kept for any sign of dissemination or the development of meningitis, it is not our custom to use antibiotics at this stage. If, however, the pyrexia should continue for six weeks even in the absence of any radiological evidence of dissemination, streptomycin and P.A.S. should be considered. If the home is inadequate then hospital or sanatorium treatment may be necessary, and, in any case, careful supervision with radiological control for at least the next two years is required. In this period the family doctor's appreciation of the situation and his recognition of apparently minor deviations from normal are all-important, for he is likely to be the first person to see the child unfortunate enough to develop miliary tuberculosis or tuberculous meningitis.

Primary Infection in Very Young Infants

There seems to be no doubt that the danger of primary tuberculous infection is related to age, and that primary infection during the first year of life is much more likely to give rise to clinical illness and to disseminate than infection after that age. Infected infants must therefore be kept under very close supervision indeed. The three most important guides are weight, temperature, and behaviour—especially refusal of feeds—irritability, or vomiting. If there is either fever or weight loss my practice is to recommend admission to hospital and administration of intramuscular streptomycin and P.A.S., even if there are no clinical or radiological signs of spread. The effect of this therapy on a child who is febrile and losing weight is sometimes, as in Case 1, most convincing. We have no fixed period for the course of therapy, the duration being judged on clinical improvement.

Case 1. Febrile Primary Tuberculosis Without Visible Dissemination

A male infant aged 8 months had been in constant contact with two tuberculous uncles. The first child in the family had died with tuberculous meningitis 18 months earlier. In November, 1950, the patient became irritable and off colour, and remained so until his admission to hospital on January 31, 1951. On admission he was thin and flabby, weighing only 14 lb. (6.4 kg.), with a fever up to 100° F. (37.8° C.) each evening. The tuberculin reaction was strongly positive and a radiograph showed a primary complex in the left side of the chest, but the cerebrospinal fluid was normal and there was no sign of dissemination. For three weeks he ran an irregular fever, unaffected by sulphonamide or penicillin. On February 21, for the first time, a few rales were heard at the base of the left chest, and a further radiograph showed that the primary focus was larger. Streptomycin was now started, and although at first the child continued to lose weight, his temperature settled and he rapidly became playful and happy. It was not until one month after the beginning of treatment that he had a reasonable gain in weight, but thereafter he steadily improved, gaining 2½ lb. (1.1 kg.) in the next seven weeks. He had 0.5 g. of dihydrostreptomycin (which at that time we were using) daily for three months. At the time of writing he is well, with a well-calcified left-sided primary complex.

Bronchial Complications of the Primary Infection

Local complications causing illness are an extension of the primary focus itself, bronchial erosion with aspiration of infection, or bronchial occlusion by granulation tissue and caseous material.

Bronchial Occlusion

Complete bronchial occlusion is sometimes only a transient phenomenon, seemingly due to simple pressure of enlarged glands on the bronchial wall. But a much more troublesome type of occlusion is produced by extension of the tuberculous process from the gland and erosion of the bronchial wall, which then is wholly or partly filled either by tuberculous granulation tissue or by caseous material, or a combination of both.

If at first the obstruction is incomplete the lobe or segment beyond becomes emphysematous, but if it fills the lumen then absorptive collapse results. Sometimes there is in addition an inflammatory change also within the collapsed area. This process slowly heals, and as it does so the bronchus becomes stenosed or distorted and the lung scarred, so that the final result is bronchiectasis. Everyone with experience of primary tuberculosis is familiar with these cases. As a rule the children have a cough, which may be hard and spasmodic if there is much bronchial irritation, or loose and productive if secondary infection has already occurred. It is in these cases that bronchoscopic removal of granulation tissue or a mass of caseous material seems to hold out hope of reopening the bronchus to allow air to enter the lung beyond. In my experience, however, it is only in the exceptional case that the lobar or segmental shadow disappears after bronchoscopy. Two possible reasons for this are that in many cases the obstruction is too far down the bronchial system to be reached by the bronchoscope, and that the segment of lung beyond is consolidated. We have therefore turned to streptomycin in the hope that by healing the granulations and assisting the absorption of pneumonic processes the lobes can be re-aerated. Here again my own experience, and that of Hutchison in Glasgow (personal communication, 1952), has been very disappointing, and we have rarely seen the re-expansion of a collapsed lung following streptomycin therapy, and "collapse" shadows not infrequently appear during the treatment of miliary or meningeal tuberculosis.

The most likely reason for this failure is that caseous material in the lumen of the bronchus remains unaffected by streptomycin, and at the same time may provide a continuing source of infection of the lung beyond. When, however, the obstruction has been removed, streptomycin will assist in the absorption of the inflammatory reaction in the lobe.

Case 2. Resolution of Aspiration Pneumonia After Coughing of Caseous Gland

A small delicate boy aged 2 years 11 months was admitted on April 16, 1951, with a history of three weeks' slight but persistent cough, with loss of energy, appetite, and weight. On examination he was seen to be an ill-looking fretful child, with alae nasi working, rapid breathing and generalized wheezing. His temperature was 103.4° F. (39.7° C.). Numerous coarse scattered rales and rhonchi were heard in both lung fields. The tuberculin test was positive. At first his temperature settled with penicillin therapy, but as the secondary infection subsided there was a constant diminution of air entry at the left base. Over the next week he became more lively, but thereafter the temperature rose and he became listless again, with a troublesome cough and sweating.

During the next 24 days his general condition remained poor, and on May 15 he had a sudden spasm of coughing and brought

FIG. 1.—Case 2. Mass of caseous material coughed up.

up a large mass of caseous material measuring $1\frac{1}{2}$ by $\frac{1}{2}$ in. (3.2 by 1.3 cm.) which on histological examination contained tubercle bacilli and many secondary micro-organisms (Fig. 1). After this incident he was acutely ill and the radiological shadow at the left base increased (Fig. 2). Streptomycin therapy was started; thereafter he improved, to make a complete recovery, the consolidation in the left lower lobe disappearing (Fig. 3). We do not yet know if any stenosis of the bronchus remains.

FIG. 2.—Case 2. Radiograph taken before treatment with streptomycin.

FIG. 3.—Case 2. Radiograph taken after treatment with streptomycin.

Bronchial Ulceration Without Occlusion

Occasionally the tuberculous process in the regional lymph nodes erodes the wall of the bronchus, forming an ulcer draining a gland. There is no blocking; instead, bacilli and fragments of caseous material are drawn into the lung beyond, forming small areas of tuberculous bronchopneumonia. These cases, though infrequent, are important; for, as shown in Case 3, they will respond to streptomycin.

Case 3. Ulceration of Bronchus, with Tuberculous Bronchopneumonia

A girl aged 4 years was admitted to hospital on December 10, 1947, complaining of pain in the back and lassitude for one month. Crepitations had been heard over the left lung anteriorly

and posteriorly, and she had failed to respond to chemotherapy at home. After her admission the tuberculin test was strongly positive, and radiological examination showed patches of inflammatory reaction throughout the left lung. Streptomycin, 0.5 g. daily, was started two days after admission. Tubercle bacilli were demonstrated in the gastric contents, and 12 days after admission bronchoscopy revealed an ulcer with raised swollen edges in the left main bronchus, 1 in. (2.5 cm.) from the carina. Histological examination of material taken from the edge revealed the tuberculous nature of the process.

Throughout January, 1948, there was a steady gain in weight, but at the beginning of February the lesion in the bronchus was still present. Streptomycin, which had been stopped for two weeks, was restarted, and improvement continued all the month, and in March there was visible improvement in the x-ray films. On April 9 the third bronchoscopic examination showed only a local reddening of the wall of the bronchus where the ulcer had been. In another week the patient was running about happily, and the last streptomycin was given on April 22, the total dosage having been 50 g. She was discharged home on April 30 and has remained well ever since.

Without streptomycin therapy this child would almost certainly have developed a progressive tuberculous bronchopneumonia of the whole of the left lung.

Treatment of Primary Infection Outside the Lung

Although about 90% of cases of primary infection occur in the lung, there remains an important group in which infection occurs either in the abdomen or in the skin or other mucous surfaces, especially those of the nasopharynx or tonsil, giving rise to a primary focus, the regional glands appearing in the neck.

Under urban conditions the abdominal primary infection is becoming uncommon, and the ascitic or plastic abdominal peritonitis is not often seen. Recently the most common manifestation of abdominal tuberculosis seen in our department has been in children with illnesses simulating an acute abdominal emergency, and the diagnosis has been made at laparotomy.

Case 4. Abdominal Tuberculosis Simulating Appendicitis

An only child, aged 5, of a good family living in an unsuitable house was admitted to hospital in December, 1950, with a history that three weeks earlier she had had measles followed by spasms of lower abdominal pain, two or three attacks each day and occasionally at night. She had not vomited and had been rather constipated. Two days before admission, at 6 p.m., while sitting in front of the fire, she had an attack of unusual severity lasting five minutes, and thereafter complained of pain on moving the right leg. The next day she was weary, and in the evening the abdominal pain began again, becoming severe on the right side.

On admission her temperature rose to 99° F. (37.2° C.), and pulse 110. In the abdomen there was marked tenderness and some guarding, but on careful palpation a mass was felt in the right iliac fossa. The summary of the history was unlike appendicitis, but the tender lump and guarding made laparotomy necessary.

At operation a large mass of caseous glands was found in the ileo-caecal region with a few small tubercles over the surface of the bowel. Intramuscular streptomycin was started, and the temperature, which reached 101° F. (38.3° C.) on the day after operation, fell to normal within 10 days. Streptomycin, 1 g. daily, was given for five weeks; the mass steadily diminished in size and the blood sedimentation rate fell from 35 on December 16, to 18 on January 2, 1951. In the next three months she gained 11 lb. (5 kg.) in weight.

My impression is that the streptomycin helped to bring about a more rapid recovery and diminished the reaction about the glands more quickly than would have been accomplished by rest alone.

Tuberculous Lymphadenitis in Neck, Groin, and Axilla

It is likely that the appearance of a large tuberculous gland surrounded by a zone of smaller satellite glands indicates that this particular gland, whether it is in the neck, axilla, or groin, is the regional gland of a primary complex in a neighbouring area drained by the glands. Careful search of the mucous membranes or skin in the area drained by the gland will sometimes reveal the focus.

Indeed, in five years I have seen more than 30 cases in which I have been able to demonstrate the primary focus in the skin, mouth, or eye in relation to the regional lymphadenitis.

Usually the tuberculous lymphadenitis appears painlessly, without constitutional upset, and the slowly progressive enlargement of the gland is discovered accidentally. Less often there is a sharp febrile reaction corresponding with the "fever of onset" in pulmonary primary infection, and the gland rapidly enlarges and becomes tender, simulating an acute pyococcal lymphadenitis.

The problem of tuberculous lymphadenitis is complex. If the gland breaks down the child will be left with a discharging lesion which will heal slowly, leaving an unsightly scar after a long period of dressing. We should therefore make every endeavour to diagnose the condition before abscess formation, while the glands are still firm and hard and the skin is unaffected. Here we are again helped by the use of the tuberculin test, by careful attention to the previous history, and by the clinical characteristics of the gland; but in many cases a period of observation will be required, for we must remember that some septic glands are not tender when first seen. The period of watching may be from one to three months, varying with the rate of glandular enlargement; but, once a firm diagnosis is made, my advice is that the regional lymph node should be removed by local dissection, leaving a neat scar which, in the cases we have so far done, does not give rise to further difficulties. Streptomycin is given for two to three days before operation and for about three weeks after. If the gland is not seen for some two years or so after its appearance and is partly calcified, the question of removal is sometimes more difficult, and I think there is greater justification for a conservative policy. Increasing size is the sign of activity, and usually close observation by doctor and parent will give enough warning to enable removal to be carried out before the skin is involved or the gland has become a soft abscess; yet sometimes, even after years of quiescence, the gland will suddenly enlarge and become a red abscess within a very few days.

Case 5. Primary Cervical Adenitis: Slowly Progressive Type

A boy aged 7 years, the fifth child in a family of six, of middle-class parents in good circumstances, was seen in January, 1951, with a history of repeated colds. There were no abnormal clinical signs and his tuberculin reaction was negative, but arrangements were made to see him again in three months.

On his second visit the situation had changed: in February he had had a febrile illness, during which a painless but persistent gland had appeared at the angle of the jaw on the left side. On examination the left tonsil was larger than the right, there was a firm painless enlargement of the tonsillar gland, and the tuberculin reaction was now positive. For another two months he was watched and the gland slowly became larger. He was finally admitted to hospital at the beginning of July, four months after the onset. Streptomycin was given for seven days and then a local dissection was made. The glands were caseous, but the wound healed well and has not given rise to any trouble since.

Streptomycin is also of great assistance in the cases of lymphadenitis with a sharp febrile response; it reduces the temperature and controls the periadenitis, so that a large gland mass will resolve into its component parts, making removal easier. Case 6 provides a good example.

Case 6. Primary Cervical Adenitis: Marked Febrile Reaction

A female infant aged 11 months, the second child in a good artisan family, had had no previous illnesses and no known contact with tuberculosis, but the family took milk neither tuberculin-tested nor pasteurized. Twenty-three days before coming to hospital she had seemed unduly listless and wanted to be nursed; two days later there was a slightly tender swelling at the angle of the jaw on the left. This was poulticed for five days, but increased rapidly in size. Since then the child had remained miserable and was difficult with her food; her general condition, however, was good. On examination her left tonsil was larger than the right, and below the left ear was a large mass of glands measuring 2 by 3 in. (5 by 7.5 cm.), smooth, firm, and slightly tender at the edges in front and behind. The overlying skin was

not involved, but the gland was fixed to underlying muscle. The right tonsillar gland was palpable but small. The tuberculin reaction was positive and the child's temperature was 103° F. (39.4° C.).

Streptomycin was started immediately, being continued for 14 days. By then the left tonsil was much smaller, practically the same size as the right, and the gland mass had shrunk to 1½ by 2½ in. (3.8 by 6.4 cm.); the component glands could now be felt. Above all, there had been a great improvement in the child's general condition. Over the next week streptomycin was continued, but the glands remained the same size, so they were removed through a crease-line incision. The wound was soundly healed one month after streptomycin was started. Eighteen months later there had not been any further trouble.

Though streptomycin has been of great assistance in the treatment of glands at all stages, I think it is unlikely to be successful in dealing with a caseous mass, and should not be relied upon to effect a complete cure.

Primary Lesions on Skin

Finally, as I have already mentioned, there are occasional cases in which a primary complex is visible in the skin. Here the effect of chemotherapy can be very much more easily observed, particularly if the primary focus itself has been at the site of a cut or other trauma. I will quote only one example.

Case 7. Healing of a Primary Skin Complex with Streptomycin

A healthy boy aged 7 cut the inner part of his left heel by treading on a piece of glass while paddling eight weeks before admission to hospital. On his return home the wound, about 1 in. (2.5 cm.) long, was dressed by his grandmother. At first healing appeared to be satisfactory, but at the end of a week the grandmother must have been dissatisfied with his progress for she applied poultices. In another week a frank but painless ulcer had formed, and this persisted until his admission. One evening, about a month after his original injury, while bathing him, his mother found a lump in his left groin. As there was no pain little notice was taken until in another fortnight the mass enlarged and became soft and red. At this stage he was taken to the doctor and sent to hospital, where the inguinal abscess was incised and the ulcer on the foot was searched for a foreign body which might explain the failure to heal. A second incision was necessary a week later, and on this occasion tubercle bacilli were found in the pus from the inguinal adenitis. At this stage I was asked to see him, and found a granulating ulcer in the heel and an open incision in the groin. The tuberculin reaction was strongly positive, biopsy of the lesion on the foot showed tuberculous granulation tissue, and tubercle bacilli had already been recovered from the inguinal gland. Here again, therefore, was the primary focus associated with regional adenitis. Approximately nine weeks after the original trauma, streptomycin, 0.5 g. daily, was started, and within five weeks both the ulcer in the foot and the gland in the groin had completely healed. Since then the boy has remained well and there has been no recurrence.

There is no doubt that this healing was hastened by the use of streptomycin, for in untreated cases of primary skin tuberculosis healing has taken many months.

The visible effect of streptomycin in primary foci on the skin and in certain cases of primary tuberculous adenitis in the neck and abdomen again brings to mind the possible effect of antibiotics upon primary tuberculosis in the chest, and raises the question whether streptomycin and P.A.S. should not be used in all cases of "fever at onset" on the analogy that a febrile response to a primary infection is likely to be associated with a marked reaction in the regional glands. This is a very fair and open question, but I do not think that an affirmative answer can at present be given: certainly in practice we would not recommend streptomycin in cases with only a febrile reaction without signs of dissemination, unless the temperature remained elevated for more than four weeks.

Conclusion

In this paper I have indicated an approach to the management of a child with primary tuberculosis and the immediately local complications. I have demonstrated that we have not yet the data to answer some of

the most important questions—for example, the risk of meningitis at different ages—and that I do not think children with asymptomatic primary infection should be treated in sanatoria unless home circumstances are unfavourable, or by antibiotics except under very special circumstances. These children should nevertheless remain under regular supervision and a close watch be kept for signs of disseminated disease. Knowledge of the primary complex is, moreover, of great assistance in detecting the early case of tuberculous meningitis or miliary tuberculosis, in which the prognosis depends almost entirely upon the time interval between onset and the beginning of treatment.

The routine use of streptomycin and P.A.S. cannot be recommended, but in cases of prolonged fever of onset, or when the infant is infected in the first year and is febrile or losing weight, or in certain cases of tuberculous cervical lymphadenitis, these compounds are of very real value.

Finally, I would repeat my plea that, wherever home care is competent and conditions are good, children with primary tuberculosis who do require treatment should be kept at home or be allowed to go home as soon as possible after confirmation of the diagnosis in hospital. This applies particularly to the child under the age of 5 years, who should be admitted to a "long-stay" hospital only when no other course is possible. We must strike a careful balance between the chance of diminishing the risk of disseminated disease and improving the child's physical state and the chance of interfering with or distorting his emotional development by long separation from home and parents.

THE CHEMICAL ESTIMATION OF CORTISONE-LIKE HORMONES IN URINE

BY

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Now that the presence of adrenal cortical hormones in both blood and urine has been detected with certainty, the problem of quantitative assay of these hormones becomes a matter of increasing importance.

In blood the presence of 17-hydroxycorticosterone and also of corticosterone has been demonstrated by several workers (Reich, Nelson, and Zaffaroni, 1950; Pincus, Hechter, and Zaffaroni, 1951), but cortisone has not so far been detected in appreciable quantity. In urine both cortisone and 17-hydroxycorticosterone (compound F) have been identified (Burton, Zaffaroni, and Keutmann, 1951b) and actually isolated by Schneider (1950, 1952). They occur in urine in association with a number of other steroid compounds, most of which are probably devoid of biological activity.

The problem of assay of these hormones in biological fluids is made difficult by the small quantities which are involved, for present estimates indicate from 5–10 µg. per 100 ml. in blood and about the same concentration in urine.

The most direct estimation is achieved by use of a biological method, since the specificity of biological responses is high. Venning, Kazmin, and Bell (1946) have developed biological estimations based on the power of these hormones to encourage glycogen deposition in the liver of adrenalectomized mice. Similarly, Cope (1951) has developed, and Cope, Boysen, and McCrae (1951) have used, a method based on the ability of these hormones to depress the count of eosinophil cells in the blood of adrenalectomized mice. Although the latter method is appreciably less laborious than the former, yet both suffer from disadvantages inherent in their biological nature. They are technically difficult to perform, they require relatively large quantities of hormone-containing extract for assay, and they are inaccurate unless large numbers of animals are used for each assay. When accuracy is increased in this way still more labour is involved and still more material is needed. The reality of these deterrent factors is well indicated by the great scarcity of published work during the past six years on adrenal hormone assays in clinical material using the liver glycogen methods. The outstanding lead given by Venning (1945) has not been followed.

Although good approximations to the hormone content of urine extracts can be obtained with much less effort by the mouse-eosinophil technique, the need for a still simpler, and chemical, method of estimation remains. The observations reported here will, it is hoped, provide the basis for such a method. The difficulties to be overcome may be divided into three main groups: (a) quantitative extraction, (b) purification from interfering contaminants, and (c) quantitative estimation by a suitable chemical reaction. Each of these may be considered separately.

Quantitative Extraction

The state of the adrenal cortical hormones in urine is such that they cannot be extracted completely by the usual lipid solvents such as chloroform. A preliminary hydrolysis is necessary to convert them into a chloroform-soluble form. The steroids probably exist in urine largely as sulphates and glucuronides (Cohen, 1951b). If the urine is acidified to pH 1 the former but not the latter are hydrolysed at room temperature. With stronger conditions of hydrolysis, such as warm acid, destruction of hydrolysed hormone may occur. Proper extraction of the hormone thus requires hydrolysis of the esters without destruction of the free hormone. Extensive studies have been made by several workers to determine optimum conditions of extraction for the formaldehydogenic steroids. The yield of these latter extracted with chloroform is increased 10 to 20 times if the urine is first hydrolysed with the enzyme β -glucuronidase (Cohen, 1951a; Daughaday, Farr, and Houghton, 1951). No studies have yet been reported on the effects of enzymatic hydrolysis on the recovery of biologically active hormones from urine, although their behaviour is likely to be similar.

Bayliss (1952), as a result of his studies on the extraction of the formaldehydogenic steroids from urine, has suggested an extraction procedure designed to recover the free hormone, the glucuronide, and the sulphate with the minimum of destruction by exposure to acid. This extraction involves three stages: (a) chloroform extraction after 48 hours' hydrolysis with β -glucuronidase, (b) immediate re-extraction after acidifying to pH 1, and (c) acid hydrolysis at pH 1 for 24 hours at room temperature and a third extraction with chloroform. In the belief that such a triple extraction represents the most complete extraction procedure at present available we have compared the yield of biologically active hormone obtained by its use with the