THE DIAGNOSIS OF OBSCURE PYREXIA

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The task of diagnosis in a patient with pyrexia of uncertain origin demands a close alliance between clinician and pathologist—an alliance based on a full understanding of each other's powers and limitations. On the one hand the clinician must have a sound knowledge of the tests which he asks the pathologist to carry out; on the other, the pathologist must not be used merely as a sort of penny in the slot machine to deliver an answer of yes or no to such questions as, 'Has this patient typhoid fever?'

Ephemeral fevers, so common, yet to which so frequently no diagnostic label can be assigned, are outside the scope of this paper, as are also the common exanthemata.

The importance of an accurate history. A careful history of the illness, especially of its onset, is of the first importance. For example, in typhoid fever the onset is usually gradual, but frequently the classical ingravescent fever with gastrointestinal symptoms does not occur and the presenting symptoms may be bronchial. Again, previous illnesses may afford a clue to the present condition, which may be a relapse, a complication, or a sequel of either a recent or a long-standing illness. Has the patient been abroad, particularly in the period directly preceding the illness? If so, the type of fever common to the foreign parts visited must be kept in mind. Are other members of the family, or fellow workers similarly affected? If the latter, Weil's disease should be considered as an industrial hazard; in this country minor epidemics have been reported among sewer labourers, coal miners, bargemen, fish workers, and tripe makers and it is important to realize that more than half the cases are not jaundiced. Usually the disease has an abrupt febrile onset followed by marked prostration, muscular pains, evidence of nephritis without oedema, frequently meningismus and marked injection of the episcleral vessels of the conjunctivae, and haemorrhages from various sites, most commonly the nose.

Particular attention must be paid to symptoms which cannot be attributed to the pyrexia *per se*, e.g., cough, dyspnoea, dysuria, or diarrhoea, which may give a direct clue to the particular organ which is diseased.

Clinical Examination

Complete and careful clinical examination is essential before any special investigations are undertaken. The whole body must be searched for a rash. The typhoid rash is ephemeral, often sparse; occasional rose spots may indeed be atypical so that their significance is overlooked. A purpuric eruption in a patient with pyrexia should particularly bring to mind septicaemias (including infective endocarditis) haemorrhagic exanthemata and the primary blood diseases.

Enlargement of lymphatic glands should obviously lead to careful examination of the area of lymphatic drainage and also to a search for other enlarged glands and splenomegaly; it also calls for a blood count to exclude the leukaemias and glandular fever. If in a patient with glandular enlargement these further examinations yield no further information, biopsy of one of the glands should be undertaken, for this is the only way of diagnosing for certainty glandular tuberculosis, lymphadenoma and lymphosarcoma. Malignant metastases or sarcoidosis may also be revealed by glandular biopsy. Occasionally the differentiation between hyperplastic tuberculosis and lymphadenoma is very difficult, even microscopically. According to Gordon, intracerebral inoculation into a rabbit of a glandular emulsion may be decisive, lymphadenomatous tissue producing a typical encephalitis.

In protozoal infections, other than Weil's disease the tongue is reasonably clean even though the pyrexia has been prolonged. On abdominal examination regard must be paid to any localized tenderness or rigidity. Tenderness and slight bulging in the loin, often without any urinary symptoms, suggest a perinephric abscess, a frequent cause of obscure pyrexia. The tenderness is very marked when the twelfth rib is pressed upon and questioning of the patient may reveal that within recent weeks he has suffered from a boil or carbuncle, an episode which often appears to the patient to be so trivial as to have passed out of his mind. Perinephric abscess is frequently bilateral.

Enlargement of the spleen rarely helps in the

diagnosis of a case of fever as it may be enlarged in almost any fever, but when extreme, points to the likelihood of a blood dyscrasia or a protozoal infection.

Rectal examination should never be forgotten. It may reveal an unsuspected pelvic abscess or a malignant growth.

Examination of the chest must be meticulous; to be on the look-out here for possible causes of pyrexia is often to get more than half-way to a diagnosis. Conditions such as rapidly advancing pulmonary tuberculosis, pulmonary abscess, interlobar empyema and chronic empyema (sometimes secondary to a bronchial neoplasm) and the atypical pneumonias, at times cause so few unequivocal signs that they are easily overlooked.

The presence of a valvular or congenital lesion of the heart in any febrile patient must arouse suspicion of an infective endocarditis and search should be made for evidence of emboli, especially in the skin (petechiae) and kidneys (red blood corpuscles in the urine, sometimes so scanty as to be recognized only by careful investigation of the centrifugalized deposit). In any suspected case repeated blood cultures should be carried out.

The nervous system must not escape attention. Nuchal rigidity is rarely well developed except in cases of meningitis. The Kernig and Brudzinski signs are, by themselves, never of great value. Cerebro-spinal fluid examination is necessary in any patient with obscure fever if positive neurological signs or nuchal rigidity are present. Very rarely in tuberculous meningitis choroidal tubercles are seen. Chameleon eye movements are possibly pathognomonic of tuberculous meningitis.

The diagnosis of acute encephalitis lethargica is fraught with great difficulties. Its possibility should be borne in mind in a patient with obscure pyrexia if any of the following signs and symptoms be present. (1) Sudden mental change in a patient previously mentally normal. (2) Ocular paresis or diplopia. (3) Any suggestion of Parkinsonism. (4) Central pain. (5) Sleep changes. (6) Involuntary movements of a myoclonic, choreiform, or athetoid type.

Focal sepsis is of little importance when considering the problem of uncertain pyrexia. Uncomplicated infection of tonsils, teeth or nasal sinuses is very rarely if ever, the cause of prolonged fever.

The presence of transverse white bands on the nails should lead to a careful scrutiny of the temperature chart, because these are often seen in association with undulant fevers, each white line corresponding to a period of pyrexia.

The type of fever may be a great help in diagnosis. Often, however, the classical terms given to the different categories of fever—re-

mittent, intermittent, continued, undulant—are incorrectly used. A remittent pyrexia is one in which the difference between the maximum and minimum temperature (usually the evening and the morning temperature respectively) is more than two degrees, the temperature being raised throughout the whole or almost the whole of the day. Most fevers, and especially those of coccal origin, are of this type. An intermittent pyrexia is one in which there are paroxysms of fever usually high and often accompanied by a rigor lasting for a comparatively short period of the day only. The temperature chart therefore shows high peaks, with subsidence to the normal line or below. The paroxysms occur daily or every third or fourth day—quotidian, tertian and quartan fevers. Malaria, pyaemias, acute pyelitis and septicaemias commonly give rise to this type of fever. A continued pyrexia is one in which the temperature remains high throughout the day with a difference between the maximum and minimum temperature of less than two degrees. In this country there are only three common causes of a prolonged continued pyrexia—the enteric group of infections, miliary tuberculosis, and infective endocarditis. An atypical pneumonia may give rise to such a continued pyrexia but its duration is rarely prolonged beyond a week. Miliary tuberculosis is often very difficult to diagnose clinically for there is usually an absence of physical signs in the lungs. A slight cyanosis is often present in these cases and should arouse suspicion.

An undulant pyrexia is one in which periods of continued fever alternate with afebrile periods. The Brucellosis group of infections, lymphadenoma (Pel-Epstein type of fever) and certain spirochaetal diseases, notably the relapsing fevers and rat-bite fever, are of this type. Malta or undulant fever may be due to *Brucella melitensis* (caprine), *Brucella abortus* (bovine), or *Brucella suis* (porcine). These types cannot be differentiated clinically. The symptoms are commonly mild and, except in the rare typhoid type, not as severe as would be expected from the temperature chart. Apart from the frequency of severe pains in the loins, limbs and joints, the symptoms are usually those common to any fever. If in a patient with pyrexia, arthritic pains with or without effusion into the joints do not respond to the administration of salicylates, the possibility of a Brucellosis infection must be considered. Sometimes gastro-intestinal symptoms including haematemesis or melaena, occasionally orchitis, and rarely jaundice dominate the clinical picture. The duration of the illness is very variable with an average of about three months, but it may be protracted for very much longer, even years. It

is important to realize that this group of infections is not always associated with an undulant type of pyrexia. Apart from splenomegaly and the occasional presence of jaundice, orchitis or skin rashes, clinical examination in patients with Brucellosis is almost invariably negative and there are no pathognomonic signs or symptoms. Particularly in the chronic group with persistent low grade fever there often cannot be diagnostically more than a suspicion that the disease is Brucellosis.

There are various relapsing fevers, e.g., *Borelia recurrenti* (E. Europe), *Borelia duttoni* (Africa), and *B. novyi* (N. America). In all these a short febrile period of four to ten days, which begins and ends abruptly, is followed after an apyrexial period of one to two weeks, by a further paroxysm. From two to ten of these relapses may occur. It is extremely unlikely that in this country a case of relapsing fever be encountered.

In rat-bite fever, in the course of a week or two after the bite of an infected animal, a relapsing type of fever develops, which may be continued for long periods. The bite itself often heals temporarily or completely and may be forgotten by the patient. The lymphatic glands draining the wound may be enlarged and frequently a maculo-papular rash appears with each succeeding paroxysm of fever. It must be remembered that the bites of cats, ferrets and other animals can cause a similar illness.

The Pel-Epstein syndrome of undulant pyrexia in lymphadenoma is of great importance because it is frequently seen in those cases where the enlarged glands or deposits are confined to the abdomen or mediastinum, and so inaccessible to ordinary methods of examination. Pyrexia in lymphadenoma is not necessarily of this undulant type, however. It may be quite irregular, with only small rises of temperature. For example, an anaemia intractable to treatment and accompanied by a low grade fever but with no other signs, may be due to lymphadenoma.

It is sometimes said that subacute infective endocarditis gives rise to an undulant type of fever, but this is not so. If the charts be carefully studied it is seen that during the apparent apyrexial periods the temperature is from time to time raised, though may be only slightly.

The pulse rate in proportion to the temperature is a point always worthy of consideration. For every degree centigrade (1.8° F.) elevation of temperature above normal, there is usually an increase of eight beats per minute of the pulse rate. In typhoid fever, Brucellosis, and in meningitis, the pulse rate is slower than would be predicted from the temperature chart. In periarteritis nodosa the

tachycardia is often very marked although the temperature may be only slightly raised.

A marked increase in the respiratory rate—pulse rate ratio in a patient with fever suggests a pulmonary infection. Here the possibility of, for example, a central pneumonia or an atypical pneumonia, may be indicated; the only localizing signs may be a diminished expansion of one side of the chest or a few crepitations. However, the atypical pneumonias do not always cause an increase of the respiratory rate.

In any obscure pyrexia, especially if there be found a collection of apparently unrelated signs, the condition of periarteritis nodosa should be considered as a possibility. The onset of the disorder is either insidious or acute in about an equal proportion of cases. The fever is usually remittent, rarely above 101° F., and there may be long apyrexial intervals. As the visceral arteries are often more affected than the peripheral, the symptomatology is very variable. Generalized weakness, loss of weight, anaemia with leucocytosis develop sooner or later, but are, of course, common to many long lasting febrile illnesses. Evidence of nephritis, with or without raised blood pressure is common, and there may be an albuminuric retinitis. The main symptoms, however, in any particular case may be cardiac, gastrointestinal, hepatic or neurological. Polyneuritis is common, but the muscles may be painful and tender even in the absence of such a lesion. Sometimes painless nodules of variable size are found in the skin or deeper tissues, and these nodules may be pulsatile. Occasionally such nodules lie along the course of superficial arteries. Mesenteric thrombosis, coronary thrombosis, Raynaud phenomenon, arthritis of rheumatoid type or with an effusion into one or more large joints, paroxysms of dyspnoea, and urticarial or purpuric rashes, have all been described in this disease. Typical lesions have been said to have been seen in patients who have had reactions following sulphonamide therapy or the administration of foreign proteins. Perhaps the condition may represent a non-specific tissue reaction, possibly allergic, rather than a disease entity. The diagnosis can be clinched by biopsy of a nodule or of a portion of a skeletal muscle such as pectoralis major.

Diffuse lupus erythematosus which has a predilection for young women, is being increasingly recognized as a clinical entity and should be considered in the differential diagnosis of every persistent unexplained remittent fever, particularly if there are protean manifestations. It is possible to have a hidden focus of lupus without the typical erythematous eruption or its characteristic

distribution on the face. The disease can cause enlargement of lymph nodes, especially of the cervical group, and splenomegaly, and also an arthritis of a rheumatoid type and effusions into serous cavities. In addition albumen and casts are often found in the urine, indicating renal involvement. In the later stages of the disease there is always a leucopenia. Diagnosis can frequently be established by biopsy of affected skin or lymph node.

The fact that the patient has been faking the temperature should be suspected if the appetite and general nutrition remain good in spite of the persistent pyrexia, or if variations of pulse rate do not synchronize with the alterations of the temperature. In such cases the temperature should be recorded rectally and a trusted nurse supervise its taking.

Laboratory Investigation

The first laboratory tests should be those of a comparatively simple nature. Perhaps the most useful immediate investigation is a leucocyte count, in that the finding of a leucopenia may go far to narrow down the issue. Speaking broadly, a leucopenia is found in the enteric and Brucellosis groups of infection, in true influenza and most of the other virus infections, in most parasitic infections, in diffuse lupus erythematosus, often in tuberculosis, and in cases in which the infection is overwhelming or the patient's resistance is negligible. Apart from primary infections, pyrexia with leucopenia is often seen in pernicious anaemia, aplastic anaemia, agranulocytosis and aleukemic leukemia.

The differential count may be of prime importance. A neutrophil leucocytosis is typical of pyogenic infections. It must be remembered that as a result of haemorrhage, a patient may exhibit pyrexia and neutrophil leucocytosis, which, incidentally, is not proportional to the magnitude of the haemorrhage. Refinements of the neutrophil count, such as those of Arneth and Schilling, are of no help in the actual diagnosis of a pyrexia of uncertain origin.

An absolute lymphocytosis is characteristic of most bacillary infections (but not of bacterium coli infection, in which a neutrophil leucocytosis is the rule). It is also marked in whooping cough and glandular fever. The latter is at times the cause of a puzzling pyrexia. In the adult there are sometimes three distinct phases of the illness. The stage of invasion lasts three to ten days and during this period the white cells show only a slight leucocytosis with a normal differential count, but occasionally there is a leucopenia. The second phase, which is often absent, is characterized by a rash, nearly always maculo-papular, resembling

that of typhoid, but occasionally (usually children) rubelliform or urticarial. In the third stage of glandular enlargement, which may last for four weeks or longer, the leucocytes increase to 15,000 to 40,000 of which 40 to 80 per cent. are mononuclear cells (normal lymphocytes and monocytes and characteristic cells which are described as either abnormal monocytes or abnormal lymphocytes). The disease often presents exacerbations and remissions and there may be a recurrence of symptoms after a long afebrile period. Rarely the mediastinal or abdominal glands are markedly enlarged causing pressure symptoms. Jaundice may be due either to enlarged glands in the portal fissure or a hepatitis (Kilham and Steigman, 1942). Recently much has been written of the neurological complications of glandular fever—non-purulent meningitis and encephalitis, and various cranial and peripheral nerve lesions. In these cases the glandular aspect of the disease is often minimal and easily overlooked. The relationship between glandular fever and benign lymphocytic meningitis is still a matter of speculation, but there is much evidence suggesting that both are due to the same organism, probably a virus. A relative lymphocytosis is seen in illness characterized by a neutrophil leucopenia.

Eosinophilia is usual in echinococcus and hookworm infections of significant degree, but these are not usually associated with fever. In trichiniasis it is nearly always present and often marked. Periarteritis nodosa, the polymyositis of which may give rise to the suspicion of trichiniasis, is often accompanied by an eosinophilia. The frequency of eosinophilia in lymphadenoma is variously stated but a figure of 15 per cent. is a fair average—not a matter therefore of particular diagnostic importance. Loeffler's syndrome of transient patches of pneumonitis (demonstrable radiologically), associated with an eosinophilia, often marked, may be accompanied by bouts of fever. The area of lung opacity may be large or small, single or multiple, may involve more than one lobe, may last from a few days to several months, and may recur at frequent or infrequent intervals over a period of months or even years. The whole condition is usually mild with little constitutional upset, but may cause a severe and protracted illness. Tropical eosinophilia, in which paroxysms of dyspnoea are usually the presenting symptom, is possibly a variant of this syndrome, and probably neither is a disease entity but merely an allergic response to various allergens derived from parasites, bacteria, drugs or pollens.

An increase of basophilic (mast) cells has no accepted significance. Any type of leukemia may be associated with pyrexia, and here a blood film and count will usually settle the diagnosis. An

exception is aleukemic leukemia, and in this condition, most commonly seen in children, a sternal puncture is necessary for diagnosis. The frequency of radiologically demonstrable bone changes in leukemia should be emphasized, and that these appearances, particularly in the long bones, may closely resemble those of acute osteomyelitis.

Sternal puncture is an important diagnostic aid of which the value is being increasingly recognized. Apart from the primary blood diseases, the presence of any of the reticuloses such as lymphadenoma, may be established. For example, an undulant type of pyrexia, unassociated with either clinical or radiological demonstrable glandular enlargement, was, by sternal puncture, proved to be due to lymphadenoma. Generalized carcinomatosis of bone, which may be accompanied by fever, can be confirmed by sternal puncture, a procedure which may also be of value in the diagnosis of infections, particularly malaria and kala-azar.

Urine.—The finding of pus in the urine is often the means of eliciting the cause of an apparently obscure pyrexia, especially in children. Pyuria is usually, but not necessarily, associated with urinary symptoms; it is well to remember that many females accept as hardly worthy of note a certain degree of smarting or scalding micturition. The necessity of a catheter specimen, especially in women, is often forgotten. Of organisms other than *B. coli* likely to be found in the urine, the tubercle bacillus is of the most importance. A tuberculous infection of the urinary tract is unlikely to be present unless there are urinary symptoms and pyuria; it should be borne in mind, also, that pus in the urine, unaccompanied by obvious organisms and yielding a sterile culture, often means that the infection is tuberculous, and demands a careful investigation of that possibility.

About 25 per cent. of enteric fever cases excrete typhoid bacilli in the urine after the second week, but this is rarely of diagnostic value. The Brucellosis organisms may be isolated from the urine in a small percentage of cases if repeated examinations are made, but here again the diagnostic value is small compared with other tests. The most favourable time for demonstrating the spirochaete of Weil's disease is after the first week of the illness, that is, late in the disease, but such examination may be successful long after the organisms have disappeared from the peripheral blood stream. The urine must be injected into a guinea-pig soon after it has been passed.

A smoky urine in a febrile patient should arouse suspicion of an embolic nephritis complicating an infective endocarditis. In many cases, however, the red blood corpuscles are so few in number that

they can be recognized only by microscopic examination of a centrifugalized deposit. Occasionally a frank haematuria in a patient with fever is caused by an intense bacillus coli infection of the urinary tract. Malignant renal tumours, though unaccompanied by infection, are often associated with pyrexia, and in these cases haematuria may be present, though not always. When malaria is suspected, the presence of urobilinuria increases the suspicion, even though no parasites are found in the blood.

Sputum. The most important examination of the sputum is that for tubercle bacilli—all too often neglected. It is unlikely that in any pyrexia of uncertain origin other organisms of significance will be found, except, perhaps fungi of streptothrix and coccidia groups.

Blood culture. A positive blood culture often clinches the diagnosis in a case of obscure pyrexia. In subacute infective endocarditis the usual causative organism is the non-haemolytic streptococcus. In this condition the blood sometimes yields culture colonies which grow only very slowly, taking over a week for a good growth. Remissions in the illness are frequent, during which bacteria may disappear from the blood, so that repeated attempts at blood culture may be necessary in a suspected case. In about 5 per cent. of cases of subacute infective endocarditis, Pfeiffer's bacillus, the pneumococcus or gonococcus is the offending organism, and in any suspected cases of this condition where the blood culture remains repeatedly negative, attempts should be made to grow these bacteria in special media.

Occasionally the meningococcus and rarely the gonococcus gives rise to a chronic septicaemia which may be very baffling. These organisms are very difficult to grow and special media are advisable. Such septicaemias are probably far commoner than is generally realized.

In typhoid fever the organism may be cultured from the blood in about 90 per cent. of cases in the first week and 60 per cent. in the second, and thereafter with rapidly decreasing frequency. Blood culture, therefore, is of greatest value in the early stages of the disease.

For the culture of Brucellosis organisms special media, aerobic conditions, extra care and great patience are all usually essential. Repeated attempts, frequent subculturing, and sometimes injection into guinea pigs may be necessary. In addition, in the case of Brucellosis aborters, CO₂ is essential for growth. Occasionally blood and material obtained from splenic puncture yields a positive result when the blood has been repeatedly negative.

Agglutination reactions. After the tenth day of the illness, the Widal is the most important

diagnostic test for the enteric group of infections. The difficulty of the Widal test is the occurrence of the anamnestic reaction, i.e., if a patient previously inoculated against typhoid develops any infection whatsoever, his Widal becomes positive and the titre of the serum increases as the disease progresses. The typhoid bacillus gives rise to three antigens, the O (somatic), the H (flagellar) and the Vi. The O agglutinin usually appears before the H and usually only the latter is present with an anamnestic reaction. But it is claimed that demonstration of the Vi agglutinin is the only certain serological sign of the presence of living typhoid bacilli and neither a previous attack nor T.A.B. inoculation will interfere with the result.

An agglutination test is the main diagnostic criterion for the Brucellosis infections. A titre of 1 in 50 is suggestive and 1 in 100 diagnostic, although much higher titres are common. A rising titre has added significance. It is important that the pathologist carries out the test up to the highest dilutions as there may be a zonal reaction, e.g., a positive at 1 in 25 and then negatives with a positive reappearing at e.g. 1 in 250. In chronic infections the agglutination tests are notoriously unreliable, the majority giving negative reactions. Proof that these are cases of Brucellosis has been made by positive culture from blood or from tissues removed at laparotomy or necropsy. It is in these cases that skin tests may be useful, and for a full discussion of their value and drawbacks the reader is referred to an article by Harris (1946).

The Paul-Bunnell agglutination test for glandular fever is probably pathognomonic and is reputed to be based on the presence of heterophil antibodies in the patient's serum in the form of agglutinins for sheep's red blood corpuscles. A single negative reaction does not exclude the diagnosis, but two or more negative tests should make the clinician carefully reconsider the diagnosis. For the diagnosis of Weil's disease many experts, particularly the Dutch, favour agglutination tests carried out with formalized cultures of various leptospira.

Examination of the blood for parasites. For the diagnosis of malaria the examination of blood films is essential and these should be both thick and thin. In any patient with an obscure pyrexia who has been exposed to malarial infection within a period of two years, this illness should be excluded. If such a patient has not been exposed to the risk of malaria for over two years, the likelihood of such an infection is remote. The presence of basophil stippling increases the suspicion of malaria. It is advisable to withhold quinine as a diagnostic test unless suspicions are very strong and thorough attempts have been made to find the parasite. A point worth remembering is that

malaria does not always give rise to an intermittent type of fever. The demonstration of spirochaetes in direct blood films is rarely possible in Weil's disease, but more often in the relapsing fevers and rat-bite fever. The blood should be injected intraperitoneally into guinea pigs, except in the case of suspected relapsing fever when the mouse is a preferable animal. The parasites may be demonstrated in the blood, peritoneal fluid or tissues of the experimental animal by dark ground illumination. As the disease progresses the likelihood of a positive result by this technique diminishes in all these infections.

Malignant disease. In about 40 per cent. of all patients with malignant tumours, fever is at some time or other present. This is commonest with neoplasms of the abdominal organs and is independent of super-added infection or metastases. Cases have been frequently recorded in which unexplained fever has been for several months the sole finding in patients with malignant disease; and because of their hidden position, renal tumours are the most frequent offenders. So, in any patient presenting an unexplained pyrexia, the possibility of neoplasm must be considered, and X-ray investigation especially of the renal and gastrointestinal tracts should be undertaken.

It is sometimes stated that there are conditions of persistent pyrexia due to interference with the nervous control of the heat regulating mechanism. This diagnosis should not be entertained. There are, indeed, many cases where the most careful investigations fail to discover the cause; most of them appear to recover. Kintner and Rowntree (1934) analysed 100 cases of long continued idiopathic fever lasting from one month to eleven years; 55 recovered after an average duration of fever of 28 months without being diagnosed, there were only seven deaths. Alt and Barker (1930) also described 100 similar cases, and in one the fever persisted for 13 years. They reached similar conclusions. Increasing knowledge has brought to notice hitherto unrecognized conditions which are the cause of previously unexplainable pyrexia.

A fairly recent example of this was the description of Q fever by Australian workers, and the subsequent discovery of the cause, the Rickettsia Burnetti. In 1945 and 1946 outbreaks of atypical pneumonia in Greece and Italy were found to be due to this organism.

Another question is whether, particularly in children, rheumatic infection can cause a prolonged and otherwise obscure pyrexia. The matter is still controversial. In conclusion, there are three points of major importance. (1) Until the correct diagnosis is definitely established, no dogmatic prognosis should be given, even though the pyrexia has persisted for a long time and con-

stitutional symptoms are profound. (2) A fatal condition such as lymphadenoma or tuberculous meningitis should never be finally diagnosed, even though strongly suspected, unless there is irrefutable proof. (3) It is always tempting to regard as tuberculous a persistent pyrexia for which no cause can be found, and so to make a diagnosis of probability on quite inadequate evidence. Tuberculosis is often the cause of long continued fever but is very rarely the cause of unexplained long continued fever. It is just as

blameworthy to label a patient as tuberculous when no such infection is, in fact, present, as to fail to diagnose tuberculosis when it is present.

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THE PRINCIPLES UNDERLYING THE ARTIFICIAL FEEDING OF INFANTS

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An apology, or at least an explanation, may be thought to be called for before adding to the already too considerable mass of print on the subject of infant feeding. This article can claim no originality, but its aim is to focus attention upon the facts which lie behind the current systems of artificial feeding of infants, and to leave aside their practical details, lucidly and elaborately expounded by other authors.

That it is desirable to feed infants at the breast is no new discovery. Until recent years the feeding of infants by breast milk substitutes was fraught with such hazards that it was little employed, and human milk from a wet-nurse almost invariably used instead.

'Fling off the useless and corrupted Juice

And teach the child the Nipple's frequent use.'

is an 18th century expression of an attitude to artificial feeding more extreme than prevails in our own time. The reasons for the failure in olden days of other modes than breast feeding are not far to seek. There was no appreciation of the organismal dangers of fresh cow's milk, and efforts to dispense with milk altogether as, for example, this German one of 1632,

'In our parts infants are given with good result broth made of beer mixed with boiled bread and butter, which is quite nourishing. Wine should not be given to infants, but in our parts beer is given to them with advantage.'

however well-suited to 'our parts,' do not seem

to modern ears to contain a germ of universal applicability. Furthermore, there was considerable opportunity for contamination of the infant's food during and after preparation, if we may judge from the following example, translated from a 16th century treatise:—

*'With milk and bread the sooty tin they fill
 Stir it together o'er the Fire and boil,
 Then try it with a touch, the Spoon they dip
 Blow it, and put it to his craving lip.'*

In short, although scattered examples in Europe of successful infant feeding with cow's milk exist from the 18th century onwards, wet-nurses were of far greater importance and required careful selection,

'Let the infant have a nurse from 25-35 years old, who is of ruddy complexion or not far from it, a moderate meat-eater also, not inclined to drunkenness but of good morals and not exercising sexual intercourse.'

for serious consequences might follow a bad choice; thus

*'Oft at a Venal Pap they suck their Bane
 And in their blood the latent Plague retain.'*

or again,

'If bad the milk the Manners may be loose.'

More recently artificial feeding, that is the feeding of infants with material other than human milk, has been of two principal types:—

1. *The use of the milk of other animals, especially the cow, though goat, ass and mare have also*