J Obs Gyn Brit Emp 1955 V-62

THE NATURAL HISTORY OF PELVIC TUBERCULOSIS

Being the Material Used for the Eighteenth William Blair-Bell Memorial Lecture

BY

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THE natural history of infection with the tubercle bacillus varies in its course from one individual to another. According to the inherent resistance of the subject, the age, sex, and possibly other factors unknown to us, the disease may reveal itself as one or more of a variety of morbid states affecting the same or different organs. These manifestations can be grouped together under different headings according to the stage in the general infection at which they appear. Ranke (1917) has referred to three stages in tuberculosis; the primary or initial stage, the secondary or generalized stage, and the tertiary stage characterized by the development of tuberculous lesions in isolated organs.

Today the various types of tuberculosis are often described as primary or post-primary (Hedval, 1948), the primary phase corresponding to Ranke's stage one, and the post-primary phase to Ranke's stages two and three. It is the latter classification which will be used throughout this paper.

Disease of the pelvic organs is merely one of the manifestations resulting from invasion of the body by the tubercle bacillus, but the place of genital tuberculosis in the natural history of this invasion is not fully understood, nor has the route by which infection reaches the pelvic organs been fully investigated. The present study is an attempt to gain further insight into the pathogenesis of female genital tuberculosis and to integrate the aetiology of this condition with the wider problem of tuberculosis in general. Throughout the paper pelvic tuberculosis is regarded as a particular manifestation occurring during the course of generalized bodily disease, rather than as an isolated gynaecological entity.

PART I

THE MODE OF INVASION

Primary infection of the female genitalia by the tubercle bacillus is now generally accepted as being a condition of extreme rarity. In nearly all cases pelvic tuberculosis occurs as the result of endogenous spread of the disease from an established focus elsewhere in the body. Dissemination may take place by the blood stream from an extra-abdominal focus situated in the lung, glands of the neck, or elsewhere, or by blood stream, lymphatic, or direct local extension from a focus situated within the abdominal cavity. It is agreed that the lymphogenous route is probably rare as this would involve retrograde permeation of the lymphatic channels.

Many authorities have regarded the lung as the most important source of the infection and von Bardeleben (1912) maintained that genital tuberculosis was invariably a secondary manifestation of phthisis. Schlimpert (1911) and Horizontow (1911) both independently showed post-mortem evidence of pulmonary tuberculosis in 90 per cent of patients suffering from the genital lesion. Many of these cases, however, were also found to be suffering from tuberculous peritonitis, and Greenberg (1921) reported the incidence of this condition among his patients with pelvic tuberculosis to be 63 per cent and Berblinger (1946) 77 per cent. In such cases the abdominal lesion has been usually regarded as the focus from which the disease had spread to the pelvis. Since co-existent abdominal and pulmonary tuberculosis is present in many cases, each having been reported in more than half the patients suffering from a

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lesion in the genital tract, one or other but not both must constitute the antecedent focus from which spread of the disease takes place into the pelvis, and doubt still persists regarding the relative frequency of responsibility of these various sites of origin. We do not yet know whether these foci are themselves primary tuberculous lesions, as in the case of a Ghon's focus, or subsequent manifestations as in the case of adult phthisis and tuberculous peritonitis. The human strain of tubercle bacillus was found in most of Jedberg's cases of pelvic tuberculosis (1950) and Liljedahl and Rydén (1950) have recently shown that 73 per cent of their patients had tuberculous lesions in the lung. Heynemann (1940) estimated 80 to 90 per cent of all cases as having pulmonary lesions, Puxeddu (1940) 78 per cent and Wegemer and Winkler (1941) 55 per cent. These recent reports are today generally regarded as proof of the pulmonary origin of the disease, although it should be noted that in all cases they come from Scandinavia or from other countries outside the British Isles, where epidemiological patterns of tuberculosis may differ considerably from those in this country particularly in regard to bovine infection; moreover in Great Britain at least it has been shown that the human strain bacillus can be isolated from 73 per cent of extrapulmonary lesions (Medical Research Council, 1949).

In the course of this investigation special reference will be made to the nature, frequency and significance of co-existing manifestations of tuberculosis which are found in systems other than the genital tract in patients suffering from the pelvic lesion. The frequency of blood-spread invasion of the pelvic organs from the lung, compared with the frequency of transperitoneal spread from a focus in the abdomen, will be demonstrated; the primary character of such a focus of dissemination will also become apparent. At a later stage in the study (Part II), a relationship will be shown to exist between the time at which a patient receives her first infection with the tubercle bacillus, and the time at which dissemination takes place to the genital tract from the site of the primary tuberculous focus. A fundamental factor which appears to decide the predisposition of the genital tract to tuberculous infection will also be demonstrated: the relationship between the menarche and the time of exposure to the primary infection.

The Material and Its Method of Treatment

The basis of this study consists of 107 consecutive cases of genital tuberculosis attending the Gynaecological Department at the Newcastle General Hospital during the past 11 years. Laparotomy had been carried out in 55 of these cases in this department. There was therefore an excellent opportunity to obtain information concerning the presence of abdominal tuberculosis in these patients. In a further 25 patients a laparotomy had already been carried out before coming under observation; in 20 patients for appendicitis, and in 5 on account of unexplained abdominal pain. Uterine curettage was performed on one or more occasions in 83 patients of this series; 71 were curetted whilst this survey was in progress. Histological examination, biological examination and direct culture were carried out in all these cases and culture was also obtained from the spleen of the inoculated guinea pig in 27 cases.

Eighty-seven of the patients in this series were radiologically examined; a substantial number of former chest films of these patients were obtained from the records department of other hospitals to which they had been admitted in the past or from the files of the tuberculosis authorities. By this means we were able to receive evidence of post-primary pulmonary tuberculosis which was active at the time the patient was under our observation, confirmatory evidence of healed post-primary tuberculous lesions which had existed in the past, or evidence of a healed or active primary complex in the lung.

The most significant information, however, was obtained through the means of a careful anamnesis conducted on all these patients in order to obtain information about the date of the primary tuberculous infection, and its situation in the body. In the course of the anamnesis we sought and frequently obtained information concerning possible contacts undergone by the patient even when there was no significant incident recollected indicating that primary infection had taken place at the time of such

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contact. The former addresses of all these patients were obtained and compared with the incidence of tuberculous infection reported from these houses and from neighbouring houses and this aspect of the study will be reported elsewhere. All events in the past histories have been verified by enquiries sent to the hospital or medical practitioner attending the patient at the time of reported illnesses, and no historical evidence has been accepted without such confirmatory evidence being obtained.

The information obtained from these investigations may be summarized as follows. (See Table I.)

(1) A past history of other forms of tuberculosis was obtained from 59 patients; 32 of these had had a pleural effusion, 22 had tuberculous peritonitis, 10 gave a history of erythema nodosum, and 5 of tuberculous cervical lymphadenitis. Seven others had sustained miscellaneous manifestations of tuberculosis.

TABLE I

Evidence of Tuberculosis in Other Systems, Among 67 Patients with Pelvic Tuberculosis

	No. of Cases
Evidence from the Medical History:	
Erythema nodosum	10
Pleural effusion	32
Tuberculous peritonitis	22
Tuberculous glands in neck	5
Tuberculous inguinal adenitis	1
Skeletal tuberculosis	3
Renal tuberculosis	1
Lupus	1
Mantoux conversion and serous meningitis associated with active primary lung tuberculosis	1
Evidence from Previous Laparotomies:	
Tuberculous glands in hernial sac	1
Abdominal tuberculosis	11
Evidence found at Laparotomy:	
Tuberculous peritonitis	13
Tuberculous peritonitis and calcified mesenteric glands	5
Calcified mesenteric glands	2
Radiological Evidence:	
Active primary complex	6
Healed primary complex	34
Active phthisis	1
Healed or doubtfully active phthisis	19
Calcified glands in the neck	3
Evidence from Renal Investigation:	
Renal tuberculosis	4

(2) The existence of abdominal tuberculosis had been noted in 11 patients at laparotomies in other hospitals; in another case tuberculous glands had been found in the inguinal sac during hernial repair. Among those who had had an appendicectomy, there had been abscess formation in 5, delayed union in 3, and fistula formation in another. Evidence of generalized tuberculous peritonitis was found at laparotomy in 18 cases; tuberculous peritonitis was associated with calcified mesenteric glands in 5 of these cases, and calcified mesenteric glands alone were found in 2 cases.

(3) Radiological investigation revealed a healed primary lung complex in 34 patients, of whom 15 had had a pleural effusion. Active adult phthisis was found in 1 patient, and radiological evidence of healed or doubtfully active phthisis in 19 patients, in none of whom had the lesion at any time been clinically manifest. Three patients were shown to have calcification of the cervical glands. The examination of previous X-rays showed an active primary tuberculous lung focus in 6 other cases.

(4) In 88 patients a full renal investigation was carried out, and of these 4 were found to have a tuberculous lesion in the kidney, otherwise symptomless.

(5) In 27 cases cultures of tubercle bacilli on Lowenstein-Jensen medium were obtained and these were all found to belong to the human strain with the exception of 1 case in which the culture was contaminated.

(6) Tuberculosis existing in systems other than the genital tract, whether in a healed or in an active state, was found by the above methods in 78 patients in all (73 per cent). If this estimate were to exclude those patients with a history of erythema nodosum or those with radiological evidence of primary tuberculous lesions in the lungs, there were then 67 patients in whom evidence of tuberculosis was found in other parts of the body (62 per cent). Of these the coexisting tuberculous lesion was active in only 8 patients (5 with renal tuberculosis; 1 with

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active phthisis; and 2 with active tuberculous peritonitis).

Discussion

Four striking features are apparent from this evidence. In the first place, the high proportion of patients in whom other forms of tuberculosis were found (73 per cent). Secondly, the large number (32) of these patients who had had a pleural effusion (30 per cent). Thirdly, the large number (32) in whom tuberculous peritonitis was found (30 per cent) and, fourthly, the fact that all successful cultures of tubercle bacilli obtained were of the human strain.

The high incidence of other forms of tubercle among these patients emphasized the fact that genital tuberculosis is not an isolated gynaecological condition, but only one of the manifestations in a generalized systemic disease; it should be remembered, however, that active tuberculosis of other systems was only found in 8 patients. An incidence of other tuberculous manifestations has also been reported in patients suffering from pelvic tuberculosis by Clayton (1952), 36 per cent; Jedberg (1950), 56 per cent; Hagen (1947), 45 per cent; and Dietel (1943), 38 per cent.

The high incidence of pleural effusion among these women is consistent with the suggestion of Sibley (1950), based upon evidence obtained from the follow-up of patients suffering from pleurisy with effusion, that this condition represents a relatively serious phase of tuberculosis. A substantial proportion of the patients in whom the primary lesion is followed by pleurisy with effusion have been shown to develop evidence of haematogenous dissemination of the disease later on. Wegemer and Winkler (1941) report that 41 per cent of their patients with pelvic tuberculosis gave a past history of pleural effusion.

In 19 patients with no previous clinical manifestation of pulmonary tuberculosis, there was radiological evidence of healed or doubtfully active adult phthisis, suggesting either a high degree of host resistance in these patients or a low virulence of the infecting organism; either of these hypotheses is consistent with the chronic nature of the subsequent lesion in the pelvis.

It may be assumed that tuberculous pleural effusion, when it occurs up to the age of 20, is associated with an underlying active primary focus in the lung. It is clear that in the patients who gave such a history (24 cases), the disease had probably spread to the pelvis from this remote focus via the blood stream, as also in those others in whom there was radiological evidence of a healed or active primary focus in the lung (35 cases), in the glands of the neck (5 cases), or primary inguinal adenitis (1 case). These data refer to 52 cases in all.

In 5 other patients caseous or calcified glands were found in the mesentery and confirmed to be tuberculous in 2 cases. These, according to the views of Rich (1951), would represent true abdominal primary lesions, and from them the pelvis might subsequently have been infected by a process of contiguous extension or haematogenous spread. In 2 other patients mesenteric glands, seen at laparotomy, were said to be calcified; but an extra-abdominal focus was also found which suggested that these glands might not in fact have been tuberculous, for double primary infection is rare. It would thus appear that there were only 5 patients who showed evidence of primary abdominal tuberculosis. The true incidence of this type of infection, however, is probably higher than this would suggest when it is remembered that not all patients in this series underwent laparotomy.

Out of 57 cases, therefore (see Fig. 1), in whom evidence of the site of the primary lesion existed, the lesion was located in the lung in 80 per cent (46 cases), the glands of the neck in 9 per cent (5 cases), the abdomen in 9 per cent (5 cases) and the skin of the lower limb in 2 per cent (1 case). The fact that a human tubercle bacillus was isolated from the endometrium in 16 of these patients lends further support to the extra-abdominal site of the majority of these primary infections for the infecting organism in 65 per cent of all tuberculous abdominal lesions in this country has been shown to belong to the bovine strain (Medical Research Council, 1949).

Approximately one-third of the patients in this series had tuberculous peritonitis, and other authors have commented on this association; Berblinger (1946) found in 77 per cent of his patients evidence of previous peritoneal tuber-

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culosis; Neu (1911) in 68 per cent; Greenberg (1921) in 63 per cent and Wetterdal (1925) in 57 per cent.

Now Haines (1952) has suggested that healed tuberculous peritonitis found in patients with pelvic tuberculosis represents a burnt out primary childhood infection with the bovine bacillus. This author maintains that subsequent genital involvement in these patients may have been caused by re-infection with the human type

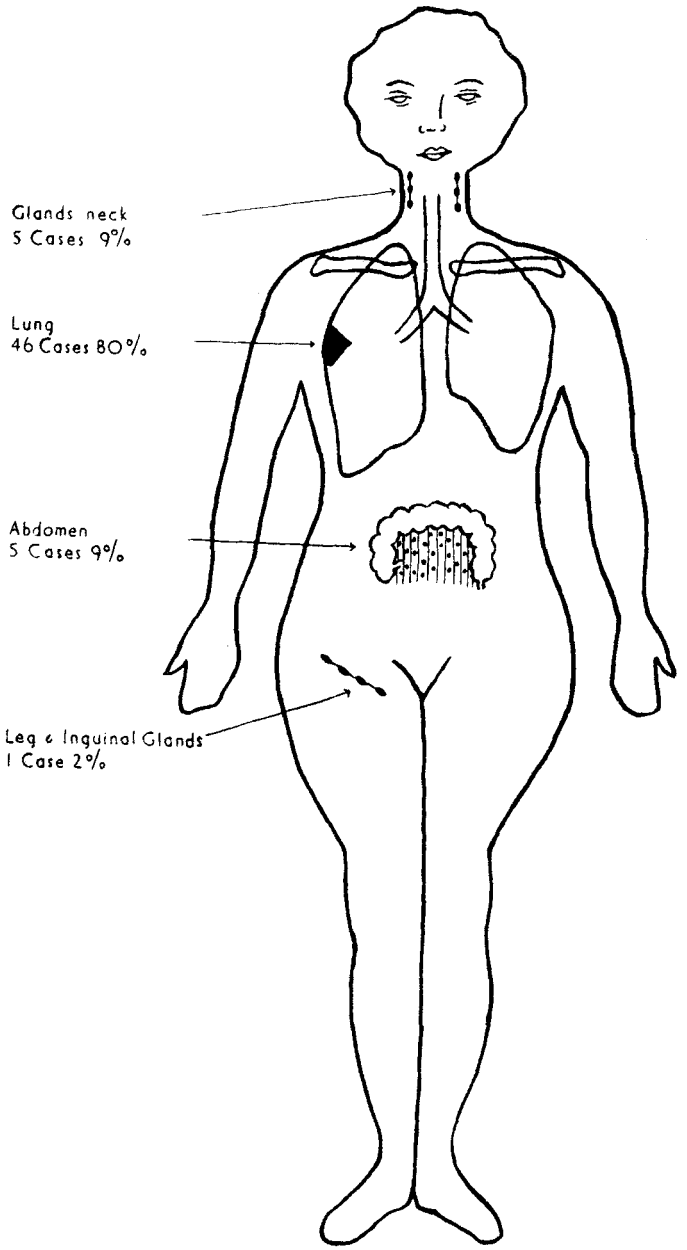

FIG. 1

Situation of the Primary Tuberculous Lesion in 57 Cases of Pelvic Tuberculosis.

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bacillus taking place during adult life. Although "primary-like" lesions which are sometimes seen in later life are supposed to be caused by re-infection of a patient in whom sensitivity to tuberculo-protein has waned (Terplan, 1940), Haines's suggestion that this may occur as early as adolescence or early maturity appears unlikely. Tuberculous peritonitis is ordinarily caused by an underlying active primary complex in the abdomen, in the same way that a pleural effusion will result from an underlying primary focus in the lung; it may also be caused by the spill of infected material from any other source within the abdominal cavity, as for example a caseating tuberculous pyosalpinx. In the past the co-existence of tuberculous peritonitis and pelvic tuberculosis has been regarded as evidence that the pelvic infection arises by transperitoneal spread from an antecedent focus within the abdomen (Krönig, 1890; Albrecht, 1911). On the other hand the idea that tuberculous peritonitis may itself have arisen by the upward local extension of a pre-existing lesion in the pelvis originated many years ago in the writings of Mayo and Mayo (1912). Haines (1952) stated this sequence of events to be not unlikely, and Boyd (1947), stating the view of most general surgeons, believed this mechanism to account for the great majority of cases of female tuberculous peritonitis.

The latter possibility has gained support from the much higher incidence of tuberculous peritonitis among females after the age of puberty. Osler (1890), in his monograph on abdominal tuberculosis, stated that peritonitis is more prevalent among females and Mayo (1929) reported 195 patients with tuberculous peritonitis of whom 153 were females. Notifications of this condition in the city of Newcastle during the past 10 years also show preponderance among females over the age of 13, by 3 to 1. The weight of this argument is lessened, however, when we consider that the attack rate for all forms of extra-pulmonary tuberculosis after the age of 15 becomes considerably higher among females than among males of the same age groups (Daniels, 1952). In the Newcastle area the preponderance among females of all forms of extra-pulmonary tuberculosis is 1·6 to 1 (Newcastle-upon-Tyne, M.O.H., 1950).

Despite this objection, however, one cannot explain the high incidence (30 per cent) of patients suffering from tuberculous peritonitis in this series in terms other than that of a process involving local extension either in one direction or the other. The relatively avascular structure of the peritoneum makes simultaneous haematogenous dissemination both to peritoneum and pelvic organs an unlikely event, and post-mortems in cases of miliary tuberculosis seldom reveal involvement of the peritoneum in the otherwise generalized dissemination.

Thirty-two patients in the present series had tuberculous peritonitis; in 5 of these the typical glandular component of an abdominal primary lesion was identified at laparotomy. In 16 cases there was evidence, either from the history or from X-ray examination, of an extra-abdominal site of primary infection; a history of pleural effusion under the age of 20 or X-ray evidence of healed or active lung primary was demonstrated in 15 cases, and tuberculous glands of the neck in 1 case. We believe that in these latter cases, in which it is reasonable to assume the absence of primary abdominal tuberculosis, the genital tract had been involved by haematogenous spread from these distant extra-abdominal foci. Tuberculous peritonitis would therefore appear to have been secondary to the pelvic lesion in these patients, the peritoneum probably having become infected by the spill of tuberculous material from the Fallopian tubes. The isolation of a human type tubercle bacillus from 10 of these cases lends support to this explanation.

Thus the evidence in this series suggests that the peritoneum had been involved by upward extension from the genital tract in 76 per cent (16 cases) of the patients in whom the site of the primary focus could be identified. Transperitoneal spread of the infection from the abdomen to the pelvic structures could only have occurred in 14 per cent of these cases. Of the two forms of extension that take place, the upward dissemination of infected material would appear to be the commoner process. This observation is consistent with the higher incidence of tuberculous peritonitis among females, and also with the finding by Kahrs (1952) who, having demonstrated a preponder-

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ance of males among those cases in which spread to the peritoneum had taken place from an abdominal primary focus, showed that the female patients in his series, who constituted the majority of the remaining cases of tuberculous peritonitis, were for the most part suffering from genital tract lesions.

PART II

The foregoing observations thus produce three very strong pieces of evidence leading to the conclusion that genital tuberculosis arises as the result of bacillaemia coming from a remote focus. In the first place, in 90 per cent of cases the known primary focus was extra-abdominal and in 80 per cent of cases that focus was in the lung. Secondly, we have indicated that there is strong evidence to support the view that, where tuberculous peritonitis was known to exist, it had resulted from upward extension of a pre-existing genital tract lesion. In the third place, in every case where the tubercle bacillus was typed, it was found to belong to the human strain, although in 65 per cent of cases of abdominal tuberculosis in this country the organism is known to be bovine (Medical Research Council, 1949).

Although bacillaemia has not so far been demonstrated in any patient suffering from genital tuberculosis, its existence in other forms of tuberculosis is now well established (Wilson, 1933; Boquet, 1935). Rich (1951) estimates that periods of bacteraemia occur in 90 to 95 per cent of all women suffering from chronic pulmonary tuberculosis. Debrés, Saenz and Broca (1934) and Rudback (1948) have demonstrated tuberculous bacilluria in children during the active period of a known primary complex. Choremis and Pantazis (1952) obtained positive bone marrow cultures from 16 out of 65 children, most of whom had an active primary complex at the time. There is increasing evidence that, when a fresh primary complex is present in the body, scattered tubercles, ordinarily few in number, can under normal conditions be found widely distributed among many organs. There is reason to believe that some of these lesions may remain quiescent for a considerable time although they contain viable bacilli, and that, during a period of lowered general resistance or of increased sensitivity of the individual organ, these foci may become active.

To quote from Rich (1951): "During the development of the primary lesion, bacilli ordinarily find their way into the blood stream whether directly from the pulmonary and lymph node lesions, or by passing through the sinusoids of the nodes and thence, by way of the thoracic duct, to the subclavian vein. In the great majority of cases the results of the bacillaemia are only sparsely scattered minute tubercles, which are eventually sterilized, and become hyalinized and absorbed. In some cases, however, viable bacilli persist in the lesions, and may later become reanimated and give rise to progressive disease of the organ in which they are situated, even though the primary lesions in the lung and regional lymph nodes remain completely arrested."

Where a hitherto unsuspected tuberculous endometritis is disclosed during investigation for infertility, it would thus appear possible that the lesion may have been present since shortly after the date of the primary infection. The time relation between the date of primary infection and the phase when dissemination takes place to the genital tract must now be considered.

Wallgren (1926) was the first systematically to investigate inter-relationships between the different manifestations of tuberculosis in the body, and was able to demonstrate a clearly defined chronological pattern correlating these various morbid states. An impressive series of reports has come from the Scandinavian countries, and to a lesser extent from Switzerland and France. In these, careful observations have been made and cases have been followed up over a period of many years from the time of development of the primary lesion. With few exceptions the later manifestations of tuberculosis are reported to occur during fairly regular time periods following the date of the initial infection. Thus the relationship between primary tuberculosis and erythema nodosum was analyzed by Wallgren (1926, 1929a); between primary tuberculosis and pleural effusion (Wallgren, 1929b); between primary tuberculosis and bone and joint infection (Wallgren, 1948); tuberculous meningitis (Wallgren and Nilsen, 1935); pulmonary tuberculosis (Wallgren, 1938); tuberculous peritonitis

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(Wallgren and Lundblom, 1935); renal tuberculosis (Beskow, 1952), and suprarenal tuberculosis (Ustvedt, 1949).

Wallgren has shown that any of the primary infections may be accompanied by erythema nodosum whether such primary be in the skin, the naso-pharynx, the conjunctiva, the lung or the abdomen. In the majority of cases, however, the primary infection gives rise to no characteristic symptoms and passes unrecognized. An early post-primary phase characterized by a tendency to generalization occupies the next 3 months and during this stage the majority of cases of miliary tuberculosis and of tuberculous meningitis take place. A later post-primary phase extends over a period of a further 4 months, during which the majority of cases of pleural effusion and of ascitic peritonitis take place (see Fig. 2).

In the case of pleural effusion and tuberculous meningitis and peritonitis, when there is an underlying primary abdominal complex, these time relationships are sufficiently constant and closely defined to make it possible from a history of one of these manifestations to identify in retrospect to within a period of 1 to 12 months the time at which the primary lesion occurred. In the case of erythema nodosum the onset of this condition will coincide even more closely (within 1 to 6 weeks) with the time of primary infection.

These concepts have recently received further confirmation during the conduct of a survey on the epidemiology of childhood tuberculosis, which has been in progress in the Department of Child Health at Newcastle during the past years (Cammock and Miller, 1953).

In the present series there were 11 cases in whom exudative pleurisy or tuberculous peritonitis was preceded by overt manifestations of active primary tuberculosis, such as erythema nodosum, or radiological changes in the lung. Investigations of the time relationship between the primary and post-primary manifestation in these patients confirms that both pleural and peritoneal effusion took place in all cases within 12 months of the primary infection (see Table II).

In this study we have accepted as reliable evidence of the date of primary infection radiological evidence of an active primary lesion in lung (6 cases); a history of erythema nodosum (10 cases); of tuberculous glands in the neck (5 cases); or in the inguinal region (1 case); of observed Mantoux conversion (2 cases); and of pleural effusion at 20 years of age or less (24 cases). The details of 37 patients to which this evidence refers are summarized in Table III.

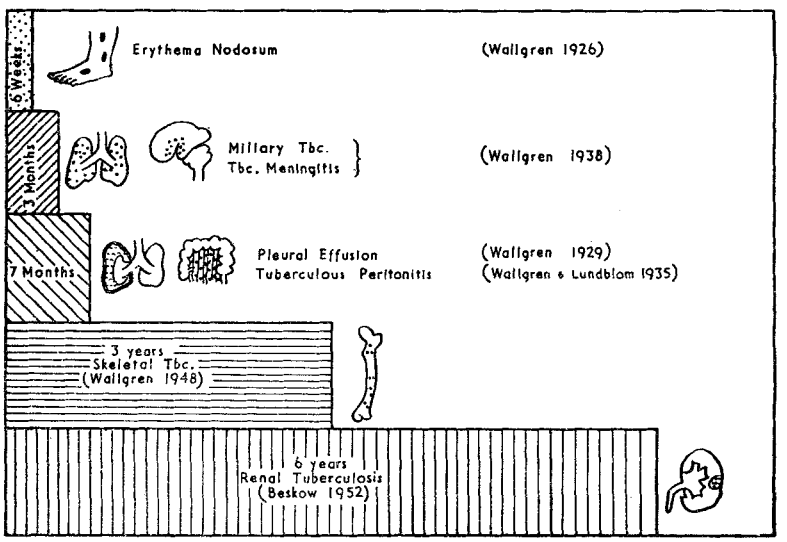

FIG. 2
Time-table of Tuberculous Infection.

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TABLE II

The Time Relationship Between Primary and Post-primary Manifestation in Eleven Patients with Pleural Effusion or Tuberculous Peritonitis

Case No.	Age at Primary Manifestation	Age at Post-primary Manifestation
3	Active primary lung tuberculosis (X-ray): aet. 19 years 11 months.	Pleural effusion, aet. 19 years 9 months: simultaneously.
4	Erythema nodosum: aet. 17 years 3 months.	Pleural effusion: aet. 17 years 7 months: 4 months after primary.
5	Active primary lung tuberculosis (X-ray) and lymphocytic meningitis, Mantoux conversion 6 weeks later: aet. 15 years 2 months.	Pleural effusion: aet. 15 years 4 months: 6 weeks after primary.
22	Erythema nodosum: aet. 12 years 6 months.	Pleural effusion: aet. 13 years 6 months after primary.
38	Active primary lung tuberculosis (X-ray): aet. 16 years 5 months.	Pleural effusion: aet. 16 years 4 months: simultaneously.
60	Active primary lung tuberculosis (X-ray): aet. 14 years.	Pleural effusion: aet. 14 years: simultaneously.
66	Active primary lung tuberculosis (X-ray): and erythema nodosum: aet. 17 years.	Pleural effusion: aet. 17 years 10 months: 11 months after primary.
99	Erythema nodosum: aet. 20 years 4 months.	Pleural effusion: aet. 20 years 4 months: simultaneously.
8	Erythema nodosum: aet. 16 years 6 months.	Tuberculous peritonitis: aet. 17 years 6 months: 12 months after primary.
94	Erythema nodosum: aet. 32 years.	Tuberculous peritonitis: aet. 32 years 2 months: 2 months after primary.
17	Erythema nodosum: aet. 13 years 6 months (approximately).	Tuberculous peritonitis: aet. 14 years 6 months: approximately 12 months after primary.

TABLE III

The Evidence from which the Date of Primary Infection was Identified in 37 Patients with Pelvic Tuberculosis

Case No.	Evidence	Case No.	Evidence
99	Erythema nodosum and pleural effusion: aet. 20.	3	Pleural effusion and X-ray evidence of active lung primary: aet. 19.
22	Erythema nodosum and pleural effusion: aet. 13.	5	Pleural effusion, X-ray active lung primary, and Mantoux conversion: aet. 15.
4	Erythema nodosum and pleural effusion: aet. 17.	38	Pleural effusion and X-ray of active lung primary: aet. 16.
66	Erythema nodosum, aet. 16: pleural effusion, aet. 17: Mantoux conversion, aet. 16: X-ray active primary lung complex, aet. 16.	60	Pleural effusion and X-ray of active lung primary: aet. 14.
8	Erythema nodosum and history of contact: aet. 16.	11	Pleural effusion and history of contact: aet. 17.
92	Erythema nodosum: aet. 32.	36	Pleural effusion and history of contact: aet. 17.
45	Erythema nodosum: aet. 14.	48	Pleural effusion and history of contact: aet. 13.
17	Erythema nodosum: aet. 13.	61	Pleural effusion and history of contact: aet. 15.
27	Erythema nodosum: aet. 11.	74	Pleural effusion and history of contact: aet. 20.
95	Erythema nodosum: aet. 15.	84	Pleural effusion and history of contact: aet. 11.
73	X-ray evidence of active lung primary: aet. 14.	18	Tuberculous cervical lymphadenitis: aet. 14.
23	Pleural effusion: aet. 19.	62	Tuberculous cervical lymphadenitis: aet. 9.
59	Pleural effusion: aet. 20.	69	Tuberculous cervical lymphadenitis: aet. 17.
24	Pleural effusion: aet. 17.	103	Tuberculous cervical lymphadenitis: aet. 12 months.
55	Pleural effusion: aet. 15.	39	Tuberculous cervical lymphadenitis and history of contact: aet. 22.
32	Pleural effusion: aet. 20.	2	Tuberculous inguinal lymphadenitis and history of contact: aet. 22.
72	Pleural effusion: aet. 17.		
76	Pleural effusion: aet. 19.		
87	Pleural effusion: aet. 12.		
90	Pleural effusion: aet. 19.		
94	Pleural effusion: aet. 19.		

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In 19 cases it was considered that there was insufficient evidence from which to deduce the date of primary infections. In 1 patient, who had facial lupus at the age of 13, no evidence of a gland component had been recorded at the time of the illness. In 8 cases of pleural effusion, occurring between the ages of 20 and 30, there was no proof that these were not secondary to adult phthisis. In 10 cases there was a history of tuberculous peritonitis with or without evidence of an abdominal primary and it is possible that, in these cases, peritonitis resulted from upward extension from a pre-existing pelvic focus. In a further group of cases there was a clearly defined history of limited intimate exposure to tuberculous infection, but there was no history of primary or early post-primary manifestation. By adopting these strict criteria, it is probable that several genuine examples of primary infection have been overlooked.

Among the 37 cases, in which there was evidence of the time of primary infection, there were only 24 per cent in which the histological diagnosis of pelvic tuberculosis was made within 5 years of the date of the primary (Table IV).

TABLE IV

Showing the Proportion of Patients in whom (i) *the Diagnosis of Pelvic Tuberculosis was Made and* (ii) *the Onset of Clinical Disturbance Due to this Condition Occurred, During Varying Time Periods Following the Date of Primary Tuberculous Infection*

Time Periods after Primary Infection	0–1 year	1–3 years	3–5 years	5–9 years	9–15 years
Proportion of cases diagnosed (per cent)	8	2	14	30	29
Proportion of cases in whom the first onset of symptoms occurred (per cent) ..	30	26	19	14	8

It was realized however that among these cases there were many in whom the infection was latent in the pelvis (42 per cent) and may have remained hidden for many years before diagnosis was achieved. Generally speaking the only complaint in this type of case was of primary infertility and this was not regarded as being a valid symptom until at least 3 years had elapsed. In certain other cases it was possible to obtain a retrospective history of other symptoms such as menorrhagia, amenorrhoea, or abdominal pain. When the date of the first clinical manifestations of the disease, including that of infertility, was considered in this way it was found that in 75 per cent of the patients, in whom the date of the primary could be identified, the onset of symptoms had occurred within 5 years of this infection, in 56 per cent within 3 years and in 30 per cent within 12 months of the estimated date of the primary infection (see Table IV). Moreover, when considering these findings it should be borne in mind that, because of the recognized chronicity of pelvic lesions, it is possible that there may have been many cases in which tuberculous infection first invaded the pelvis even sometime before clinical disturbance was manifest.

Now there is considerable evidence that intermittent bacillaemia accompanies the period of activity of primary tuberculous lesions (vide supra). In most cases, because the primary lesion is healed within 12 months of its initiation, bacillaemia and its attendant risk of dissemination ceases after this time (Wallgren, 1948). Thus post-primary manifestations would be expected to result from dissemination taking place within 12 months of the initial infection. The time relationships which have been demonstrated between the date of primary infection and the onset of first clinical disturbance due to genital tract infection are thus consistent with the conclusion that invasion of the pelvic organs occurs soon after the patient received her primary infection.

Although in the majority of cases (56 per cent) the onset of clinical disturbance is to be expected within 3 years or so of this event, many cases remain in whom symptoms are not sufficiently marked to lead to the recognition of the disease at this early stage. Table IV, which demonstrated these time relationships however, includes many patients in whom the onset of symptoms, and the establishment of the histological diagnosis, took place within only 12 months of the patients having received their primary infecting dose of tubercle bacilli.

Winkler and Wegemer (1940) state that tuberculous salpingitis is manifest most often

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within 5 years of a pleural effusion. Hagen (1947) demonstrated that one-third of his cases of genital tuberculosis showed their first symptom within 1 year, and two-thirds within 5 years of pleural effusion, and Jedberg (1950), in a recent survey of 186 cases of pelvic tuberculosis, found that 20 per cent of his patients developed their first symptom within the year and two-thirds within 5 years of the initial manifestation of the disease. It must be noted that Jedberg's cases include many which were rejected from this series as not being necessarily primary manifestations.

The findings reported by the above authors are in agreement with those in the present series which suggest that pelvic invasion probably takes place during the early post-primary phase of the infection. The onset of symptoms in female genital tuberculosis can therefore be expected to begin within 3 years of the primary infection in the majority of cases and it is suggested that, at whatever time in life the diagnosis of pelvic tuberculosis is made, the disease has probably been present in the genital tract since before the time at which healing of the primary lesion occurred.

These conclusions are convincingly illustrated in the following case histories:

Case No. 5

Age 13	Menarche.	
Age 14$\frac{9}{12}$	Mass X-ray on leaving school:	no lesion seen in chest.
Age 14$\frac{11}{12}$	Conception.	
Age 15	10th week of pregnancy:	benign lymphocytic meningitis (Green's active primary lesion in chest), syndrome. Mantoux negative.
	16th week of pregnancy:	Pleural effusion. Mantoux positive.
	29th week of pregnancy:	Ante-partum haemorrhage, premature onset of labour; fresh stillbirth; post-mortem examination; normal foetus.
	9 weeks after delivery:	Mass palpated in right Fallopian tube. Biopsy—*Tbc. cervicitis, Tbc. endometritis.*

Conclusion: Histological diagnosis of pelvic tuberculosis within 6 months of primary infection.

Case No. 8

Age 12	Menarche.
Age 16	Exposure to pulmonary tuberculosis contact. Erythema nodosum.
Age 17	Tuberculous peritonitis. Mantoux positive. Onset of mittelschmerz and irregular menstruation.
Age 21	Sought medical advice complaining of above symptoms. Histological diagnosis of *Tbc. endometritis.*

Conclusion: Histological diagnosis of pelvic tuberculosis 5 years after primary infection. Onset of symptoms one year after primary infection.

Case No. 16

Age 14	Menarche.
Age 19	Marriage. Intimate exposure to tuberculous infection.
Age 24	Right pleural effusion. Onset of bloodstained vaginal discharge and heavy irregular episodes of uterine bleeding.
Age 25	Histological diagnosis of *Tbc. endometritis* and *Tbc. cervicitis.* Chest X-ray: healed primary complex, right lung.

Conclusion: Histological diagnosis of pelvic tuberculosis within 12 months of probable primary lung infection.

Case No. 66

Age 14	Menarche.
Age 16	Erythema nodosum. Active primary lesion in chest.
Age 17	4th month following erythema nodosum: Mantoux test negative.
Age 17	Mantoux test positive.
Age 17	Left pleural effusion. Onset of irregular episodes of bleeding.
Age 17	Unilateral tubovarian mass. Histological diagnosis of *Tbc. endometritis.*

Conclusion: Histological diagnosis of pelvic tuberculosis one year after primary infection.

Case No. 3

Age 16	Menarche.
Age 19	Left pleural effusion: active primary lesion in chest. Marriage during same year.
Age 20	Tbc. peritonitis.
Age 21	Routine infertility investigations. Histological diagnosis of *Tbc. endometritis.*

Conclusion: Diagnosis of pelvic tuberculosis within 2 years of primary infection.

A further interesting observation emerges from the study of the ages at which primary tuberculous infection took place in the 37 patients in this series.

Table V shows that in the majority of cases primary tuberculous infection had occurred late in life, coinciding in most patients with the period of adolescence or early maturity.

When the time interval elapsing between the patient's age at the menarche and her age at

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TABLE V

Age at the Time of Primary Tuberculous Infection in 37 Cases of Pelvic Tuberculosis

Age at Primary Infection	0–4 years	5–9 years	10–14 years	15–19 years	20–24 years	24 and over
Number of Patients ..	1	1	10	18	6	1

the time of primary tuberculous infection was estimated in each of these 37 cases, it was found that in 46 per cent the primary lesion was established within 2 years of the menarche, and in 70 per cent within 4 years of this event (see Table VI).

TABLE VI

Showing the Association Between the Age of Individual Patients at the Time of Their Primary Infection and Their Age at the Menarche

Length of Time Interval Between Menarche and Primary Infection	Number of Cases	Per-centage
Primary infection occurring during same year as menarche	3	8·1
Primary infection within 2 years of the menarche	17	46
Primary infection within 4 years of the menarche	26	70
Primary infection within 6 years of the menarche	31	85
Primary infection occurring within longer than 6 years after the time of the menarche	37	100

The report on the Prophit survey (Daniels *et al.*, 1948) showed that 63 per cent of the young adult group in this country (1935 to 1944), aged 15 to 16, had already received their primary infection; the recent survey by the Medical Research Council (1952) showed that 55 per cent of girls in the urban areas in the North of England including Tyneside had undergone Mantoux conversion by the age of 15.

The remarkable fact has therefore been demonstrated that in the patients in this series who were suffering from genital tract tuberculosis, the age distribution of tuberculous primary infection is directly contrary to the normally expected age distribution for this event among people living in the Newcastle-upon-Tyne area.

If the majority of individuals living in Newcastle receive their primary tuberculous infection during childhood, and if, as we have shown in this study, genital tuberculosis is an early post-primary manifestation of the general invasion of the body by the tubercle bacillus in which the majority of patients may be expected to manifest their first symptom within 3 years of this event, then it is to be expected that pelvic tuberculosis would be diagnosed among children in this area.

A search made of the clinical records of the gynaecological department at the Newcastle General Hospital, and of the records of the department of child health at the Royal Victoria Infirmary during the previous decade, 1942–1951, failed to discover a single female patient under the age of 12 years having been admitted to either unit with a diagnosis of genital tract tuberculosis.

This search was extended to the post-mortem records of all female children dying under the age of 12 years during this 10-year period. Five hundred and sixty-two autopsy reports were examined in this way, many on children who had died from tuberculous meningitis, a bacillaemic form of tuberculosis. Only one case was found, a child dying from miliary tuberculosis, in whom a tuberculous lesion was identified in the genital organs; this child, however, who died at 10 years of age, may be said already to have been approaching the adolescent period of life.

An examination of the literature by Kelly in 1901 showed only 20 cases of genital tuberculosis to have been reported in children up to that date.

Thus it appears that, when primary tuberculous infection occurs during childhood, there is little or no risk of subsequent dissemination to the genital tract taking place. When primary infection and post-primary tuberculous bacillaemia coincide with the period of adolescence or early maturity, however, there would appear to exist at this time a special vulnerability of the female genital tract to invasion by the tubercle bacillus.

If confirmation of these findings is forthcoming from other centres, there would appear

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to be grounds for suggesting that those girls who are Mantoux negative by the time they reach the age of 11 should be rendered positive by B.C.G. inoculation. Tuberculous meningitis, which is a particular risk accompanying primary infection in early childhood, has been reduced or almost eliminated in Scandinavia by the adoption of B.C.G. inoculation; genital tuberculosis, which results in sterility, appears to be the particular risk of primary infection in adolescence, and this might also be reduced or eliminated by taking similar steps.

Summary

(1) The mode of invasion of the genital tract in 107 women suffering from pelvic tuberculosis has been investigated.

(2) A high proportion of patients (73 per cent) showed evidence of other forms of tuberculosis; pleural effusion and tuberculous peritonitis each occurring in approximately one-third of the cases. In only 8 patients were these co-existing lesions still in an active state.

(3) The primary site of tuberculous infection was located in 57 patients; this was found to have been in the lung in 46; in the glands of the neck in 5; in the abdomen in 5; and on the skin in 1 case. This suggests that invasion of the pelvis had taken place by the haematogenous route in at least 52 (90 per cent) of these patients.

(4) Evidence of the site of the primary was available in 20 patients who had had tuberculous peritonitis. In only 1 out of every 4 of these cases was the site of this primary within the abdomen. It would therefore appear probable that peritonitis had arisen in at least 75 per cent of these patients as the result of spread of infected material from a pre-existing tuberculous focus in the pelvis.

(5) The infecting organism was found to belong to the human strain tubercle bacillus in all cases in which culture was successful.

(6) The date of the primary infection was identified in 37 patients. A relationship has been shown to exist between the time at which the patient receives her first infection, and the time at which the infection proceeds to invade the genital tract from this primary source. In many cases it is only a matter of a few months before the invasion occurs; in more than half of the patients (56 per cent) there was evidence that pelvic infection had taken place within 3 years of the primary. From this evidence it is believed that dissemination to the pelvis probably takes place during the period of activity of primary tuberculous lesions.

(7) Genital tuberculosis is shown to be a particular risk accompanying primary tuberculous infection during adolescence. It has been suggested that this should provide additional grounds for urging that girls be rendered tuberculin positive by B.C.G. inoculation before reaching this age.

I wish to acknowledge the close collaboration given to me in the conduct of these investigations and in the preparation of this paper by Mr. Linton M. Snaith, M.D., M.S., F.R.C.S., F.R.C.O.G., who put at my disposal the clinical material which has been used in these studies.

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