Family History

In this series of 145 cases there are two families (one out of 72 families) in which another sibling or parent has had an intussusception. MacMahon (1955) calculated that the eight affected families in his series of 396 cases (one out of 50) represented a familial incidence 40 times greater than would have been expected by chance. Although less marked, the familial incidence in the present series still is much greater than can be accounted for by a random occurrence of intussusception, and the figure has been derived simply from a review of case records. Detailed field inquiries, as carried out by MacMahon, might well reveal more affected families. In one of the two families noted the father, a general practitioner, had suffered from a recurrence of his intussusception, and a similar double misfortune befell his son.

Discussion

The incidence of acute intussusception in the City of Aberdeen (1.81 per 1,000 live births) is only slightly greater than that in Birmingham and Edinburgh. The accuracy of ascertainment of cases is probably the same in all three regions and in Newcastle, since the reported incidence of congenital pyloric stenosis (approximately 3 per 1,000 live births) is the same in each of them (Davison, 1946; MacMahon *et al.*, 1951; McLean, 1956; Smith, 1960). The significantly greater incidence in the rural areas is unexplained, but it is still little more than half the Newcastle figure.

Intussusception may result from a congenital predisposition being triggered off by an acquired agent. The male preponderance and the increased incidence of intussusception among relatives may be accounted for by some inherited predisposition or abnormality such as excessive quantity or reactivity of alimentary lymphoid tissue. It is difficult to account for them by any other theory. At the same time an acquired agent seems the most likely explanation for intussusception occurring in small outbreaks lasting a few months. The nature of the acquired agent is unknown, and it may not be pathogenic in ordinary infants. The unusually large size of the mesenteric lymph nodes suggests that they may react vigorously. No known bacterium has been found blameworthy; information is being collected about adenoviruses to determine whether or not they play any part in the aetiology of intussusception.

The increased incidence in the rural areas is not fully explained by either part of this suggested dual aetiology. Inbreedings could increase a congenital predisposition. On the other hand, failure of the infant to become immunized either passively or actively at a very early stage of its development to a relatively innocuous external agent such as an adenovirus may render it more susceptible to that agent at the age of a few months.

Summary

The incidence of acute intussusception and the age-and-sex distribution and family histories of the 145 patients seen in North-east Scotland from 1950 to 1959 have been determined.

The overall incidence is 2.19 per 1,000 live births; the incidence is significantly greater in the rural area than in the City of Aberdeen.

The male preponderance is less marked than in other regions, but the sex differential is still highly significant.

When analysed for periods of six and twelve months, intussusception occurs in a non-random manner.

These findings suggest that acute intussusception results from a congenital predisposition being triggered off by an acquired agent, possibly an adenovirus.

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TWO INCIDENTS OF TUBERCULOUS INFECTION BY MILK FROM ATTESTED HERDS PUBLIC HEALTH AND CLINICAL ASPECTS

BY

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This report describes two recent incidents where tuberculous infection occurring in children was apparently related to the consumption of milk from attested herds.

First Incident

In July, 1959, a routine tuberculin test of an attested dairy herd in Oxfordshire revealed six reactor cows. These animals were removed and slaughtered, and on post-mortem examination one animal was found to have a tuberculous udder. The herd was retested in September, 1959, when 19 animals were found to be positive reactors. These animals, together with a few doubtful reactors, were slaughtered, the result being the destruction of the entire milking herd. The cause of the breakdown in the herd was not established, but it was suggested that a cow which had been sold off the farm to a knacker, prior to July, 1959, may have been the originator of the herd infection.

The bulk of the milk from this herd had been sent daily for pasteurization before retail to the general public.

In November, 1959, a general practitioner informed the medical officer of health for Oxfordshire that a girl

aged 5 years, living in one of the farm cottages, had developed erythema nodosum and that her sister, aged 7 years, reacted positively to a 1:1,000 tuberculin test. These girls came from a family which had received a daily supply of untreated milk from the herd in question. The other members of the family—mother, father, and a third sister—were seen at the chest clinic. All had positive tuberculin tests (Heaf type). Their chest x-ray films were satisfactory and they were all well and free from symptoms.

Inquiries revealed that a second family, living in an adjoining farm cottage, had also received a regular supply of raw milk. The members of this family were examined at the chest clinic. The mother, father, and two sons aged 2 and 4 years had positive Heaf tests, but the baby aged 6 months, who had been fed on national dried milk, was Heaf-negative. Members of the farmer's family, who were the only others consuming the raw milk, gave the following Heaf results: mother was negative, and father and two sons aged 15 and 16 years were all positive.

Because of the clear-cut history of recent exposure to infection the positive tuberculin reactors were each given a six-months course of antituberculous chemoprophylaxis. The adults received isoniazid 300 mg. daily and sodium P.A.S. 12 g. daily. The children received doses appropriate to their age and weight; these varied between 2 and 4 g. of P.A.S. daily, and between 50 and 100 mg. of isoniazid daily. No toxic reactions occurred in the above group.

This incident had limited consequences in that only three families were regularly supplied with untreated milk from the affected herd, but it did serve to alert both the veterinary and the public health authorities to the possibility of tuberculous infection occurring in attested herds with consequent danger to the consumers of raw milk.

Second Incident

In December, 1959, the medical officer of health for Oxfordshire was informed by the divisional veterinary officer that a cow originating from attested premises in the county had subsequently been slaughtered in London and had been found to be affected by tuberculosis. The hind quarters and offal were condemned, but there was no macroscopic evidence of tuberculosis of the udder.

The origin of the animal was a self-contained Friesian herd which had been attested since 1947. The last positive reactor had been found in 1951. The herd was last tested in June, 1959, when all the animals, including the one in question, were found to be negative.

The history of the animal revealed that she had suffered from clinical mastitis in one-quarter of the udder in September, 1959. None of her milk was thenceforward used for human consumption, but milk from the apparently healthy quarters of the udder was fed to calves. As the mastitis did not clear up the cow was dried off and sold.

A herd tuberculin test was immediately carried out, and this revealed 35 positive reactors and 6 inconclusive reactors. The reactors comprised 1 bull, 12 cows, and 22 calves. Three of the calves were approximately 3 months old and 19 were 4 months old. All the calves under 3 months old and over 4 months old passed the test. None of the calves which had received milk from the three apparently healthy quarters of the udder reacted to the test.

The history and the result of the tests suggested that this cow had been excreting tubercle bacilli in her milk for about six weeks before the development of clinical evidence of mastitis in September, 1959.

All the reacting animals were slaughtered and post-mortem examination revealed glandular involvement in 18. Macroscopically affected lymphatic glands examined by the Ministry of Agriculture's laboratory at Weybridge were reported positive for tubercle bacilli which were typed as bovine strain.

It was ascertained that the bulk of the milk from the herd was sent for pasteurization, but that about 20 gallons (91 litres) of untreated milk were retailed daily in the adjoining village. A list of consumers was obtained and the general practitioners in the area were informed of the situation.

After consultation with the chest physician it was decided to tuberculin-test all children and young persons up to the age of 21 years who might have consumed the untreated milk. The consent of parents was obtained by house-to-house visitation by health visitors and tuberculin tests by the Heaf method were carried out early in January, 1960. The results are shown in Table I.

TABLE I.—Result of Tuberculin Tests

	No. Tested	Total No. of Tuberculin-positive Reactors			Total No. of Negative Reactors
		History of Previous Positive Reaction	History of B.C.G. Vaccination	No History of Positive Reaction or B.C.G.	
Pre-school	50	—	1	20	29
At school	92	3	13	42	34
Left ..	18	—	9	4	5
Total ..	160	92			68

Of the 23 children who had had previous B.C.G. vaccination, 10 had strongly positive Heaf reactions (+++) or (+++), indicating very probably a superimposed infection.

All the positive reactors were examined at a series of special clinics held by the chest physicians. At the first examination two of the children, a boy aged 5 and a girl aged 13, were found to have unilateral enlargement of tonsillar lymph nodes. Of the 92 positive reactors, 85 accepted the offer of a prophylactic course of "pycamisan 33" according to the following dose schedule:

Age in Years	No. of Cachets Daily	Age in Years	No of Cachets Daily
Under 2 ..	1	12 and under 14 ..	6
2 and under 4 ..	2	14 and under 16 ..	8
4 and under 7 ..	3	16 and over ..	9
7 and under 12 ..	4		

Each cachet of pycamisan 33 contained 1.5 g. of P.A.S. plus 33.3 mg. of isoniazid.

The girl aged 13, mentioned above, had some difficulty in taking the treatment because of nausea and loose bowel movements. Her treatment was interrupted and other forms of P.A.S. had to be tried. After three months the gland broke down to abscess formation and was operated on. The pus from the abscess contained acid-fast bacilli on the direct film, but, unfortunately, tubercle bacilli were not grown on culture and so the type of the bacillus was not determined. The boy aged 5 is progressing satisfactorily.

Twin girls aged 4 years who had been living in the village were traced to the area of another authority and on examination both were found to be tuberculin-positive; one child had enlarged cervical glands, and both had hilar enlargement on x-ray examination. Both

have since been admitted to a chest hospital. In each case gastric lavages were negative for tuberculosis on culture, but guinea-pig inoculation in both cases showed evidence of tuberculosis. Unfortunately, no positive cultures could be obtained from the guinea-pigs, and so the type of *Mycobacterium* is not known. On careful inquiry the only possible source of infection that could be discovered was the milk.

Of the 85 patients treated, several failed to take the full course because of various upsets. Table II gives a brief outline of the toxic effects noted.

TABLE II.—*Toxic Effects of Treatment*

Toxic Effects	No. of Patients	Ages	Result
Slight nausea	6	4-15	Treatment continued
Missed "quite a few" cachets	1	13	
Nausea	3	14-16	Stopped all treatment after 3 months
	2	14-18	Stopped all treatment after 1 month
Dermatitis	1	10	P.A.S. stopped. Isoniazid continued alone
Peripheral neuritis ..	1	17	Treatment stopped
Lassitude and evanescent rash	1	13	Treatment continued
Initial temporary depression	2	9-10	
Jaundice and rash ..	1	5	Treatment stopped

Seven patients had to stop the treatment prematurely. Six patients admitted that they failed to take the drugs on occasions. Eight patients had some degree of upset but managed to complete the course.

It is almost certain the P.A.S. caused the toxic symptoms in 8 of the 85 cases treated, and in view of the investigation reported by Poole and Stradling (1960) one wonders how many more failed to take adequate dosage. Those workers noted that 6 of their 32 patients failed to take P.A.S. and that 9 others were so unco-operative in other ways that their intake of P.A.S. was suspect.

Discussion

Public Health Aspects

Incidents such as those recorded are, fortunately, not common nowadays. Hallo (1950) described infection among 100 young children and babies, the source of which proved to be milk from a farm with an attested herd, the last inspection of which had taken place six months previously when all the cows had given negative reactions to the tuberculin test. Subsequent testing of the herd revealed that 66% of the animals had become positive reactors. The source of infection of the herd could not be found. Faulds (1945) described a case of tuberculous meningitis in a child who had lived on a farm and who had received milk which was not heat-treated; the herd from which the milk came was apparently free from clinical tuberculosis at a routine examination. When this milk seemed by the history to be incriminated an examination of the animals revealed one cow with open tuberculosis of the udder, and a sample of the milk contained large numbers of tubercle bacilli. Wynne Griffith (1960) described an incident where the finding of positive tuberculin reactors in two young children was attributable to their drinking milk from a tuberculin-tested herd in which positive reactors had been discovered.

Recently the area eradication plan for attested herds has been extended to cover the whole country, and the incidents reported above may serve to warn against the false sense of security to be derived from the fact that

future milk supplies will emanate entirely from attested herds. It is our experience that the designation of milk as tuberculin-tested cannot in the absence of pasteurization guarantee freedom from the presence of tubercle bacilli.

It is felt also that the notification of childhood tuberculosis warrants the most careful investigation into the source of the patient's milk, and where the latter has been consumed untreated the investigators should not be deterred from further search by the fact that the milk was designated as tuberculin-tested.

The prompt notification to the medical officer of health of tuberculous disease, in humans or in animals, is important. Our attention was drawn to the first incident as a result of an astute clinical observation by a general practitioner, who had noticed the relationship between the tuberculous infection in the herd and the infection in the children. The second incident demonstrates the value of close co-operation between the divisional veterinary officer of the Ministry of Agriculture and the county medical officer. In this case the divisional veterinary officer notified the county medical officer of the history of an animal slaughtered many miles outside the county, thus initiating the inquiry which is described above.

It may be useful to comment on the frequency with which attested herds are tuberculin-tested. At present the interval between tests is one year, although this may, in certain circumstances, be extended to two years. In addition, newcomers to the herd are tuberculin-tested as they arrive. Routine tuberculin-testing is carried out on the instructions of the Ministry of Agriculture. In both incidents reported above, a very rapid dissemination of infection took place in the herds once tuberculosis had been introduced. It might be advisable, therefore, if tuberculin tests could be carried out either at more frequent intervals or on each occasion when sickness in the herd cannot be clearly diagnosed as being non-tuberculous.

Clinical Aspects

Bacteraemia is almost invariably present in primary infection. Guggenheim (1931) reported that he found abortive tuberculous haematogenous disseminations in 10% of 7,000 necropsies. The tuberculosis was noted as an "accidental finding," and so the percentage is a minimum one.

Foci may remain latent for many years and then produce bacillaemia and tuberculous lesions in various parts of the body, such as the lungs, meninges, bones and joints, and genito-urinary tract.

According to Kayne *et al.* (1948) malignant tuberculosis due to bovine tubercle bacilli is well known.

Davies (1960), reporting on the natural history of children exposed to mycobacteriosis, stated that between 1932 and 1950, 2,500 children were observed at the Brompton Hospital contact clinic and none had chemotherapy or B.C.G. vaccination: of 1,567 who were tuberculin-positive, 735 (47%) developed lesions. Among other things, he concludes that recent tuberculin conversion is an indication for treatment, especially during infancy and adolescence.

Many authors have shown that there is a risk of developing serious extrapulmonary tuberculous lesions after tuberculin conversion (Gedde-Dahl, 1948; Nissen Meyer, 1949; Anderson *et al.*, 1951¹; Thompson, 1952; Cammock and Miller, 1953; United States Public Health Service, 1957).

The United States Public Health Service (1957) reckon that isoniazid is 80% effective in preventing serious extrapulmonary complications. The follow-up is short, being at the most 30 months.

In the second outbreak mentioned, the bovine strain of tubercle bacilli was found in the slaughtered cows and, as no human source of infection could be found after an intensive search, it is reasonable to conclude that almost certainly the herd infection was due to a bovine source. One must also infer that the high percentage of tuberculin-positive reactors who had been consuming the herd milk, were also infected with the bovine strain of tubercle bacilli.

The dangers of recent and late disseminated tuberculous foci as described led to the decision that chemoprophylaxis should be given. From a long-term point of view nothing is known of the value of such prophylaxis, but the administration of isoniazid seems very worth while as it is an effective anti-tuberculous agent and as it diffuses into all tissues and fluids and into dense caseous lesions in high concentration (Barclay *et al.*, 1953).

To reduce the risk of resistant tubercle bacilli the isoniazid was combined with P.A.S. It would appear that children do not tolerate P.A.S. much better than adults and that preparations of the pycamisan type are not very suitable for mass prophylaxis.

Conclusion

The finding of a high percentage of positive tuberculin reactors among persons who had recently ingested untreated milk derived from tuberculin-positive cattle led to the decision that treatment should be offered to reduce the risk of subsequent disseminated tuberculosis.

The chemotherapy had untoward effects in an unexpectedly large number of children and so the dangers of inadequate treatment and dosage are very real. We believe that prophylactic treatment requires as careful supervision as routine therapy.

Close liaison between the Ministry of Agriculture, the medical officer of health, and the chest physician is of paramount importance. It is essential that the medical officer of health should be informed at once of any possible tuberculous infection which might directly or indirectly endanger the milk supply, so that appropriate public health measures may be instituted.

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THERAPEUTIC EFFECT, UTILIZATION, AND FATE OF INJECTED VITAMIN B₁₂ IN MAN

A PRELIMINARY REPORT

BY

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During studies on the utilization of injected vitamin B₁₂ in man, it was observed that an injection of 1,000 µg. of vitamin B₁₂ given intramuscularly did not maintain the serum vitamin B₁₂ level above the pre-injection level, or above the lower limit of normal, for much longer than an injection of 50 or 100 µg. given intramuscularly. It seemed likely that this might be due simply to the increased amount excreted after the larger injection. Detailed investigations, however, have shown that this is not the case and that the duration of effect of a large dose of vitamin B₁₂ is much less than might be expected from the duration of effect of a small dose, even when allowance is made for the amounts excreted after injection.

Observations made on six patients which demonstrate this phenomenon clearly form the basis of this paper.

Patients, Materials, and Methods

The diagnosis of Addisonian pernicious anaemia was established in all patients on the basis of a macrocytic anaemia, megaloblastic bone-marrow, histamine-fast achlorhydria, low serum vitamin B₁₂ level, and response to parenteral vitamin B₁₂ only when they first came under observation. Absorption studies with radioactive vitamin B₁₂ alone and with intrinsic factor were performed in all cases and confirmed the diagnosis. The patients were treated with parenteral vitamin B₁₂ for several months, and then treatment was withheld and the serum vitamin B₁₂ level estimated regularly. When the level fell to an arbitrary figure, usually about 140 µg./ml., which is the lower limit of normal by the method used, the patient was given an injection of Co-58 vitamin B₁₂, 1,000 µg. 0.2 µc, or 100 µg. 0.2 µc, or 50 µg. 0.3 µc. The urine excreted in the subsequent 24 hours was collected, the radioactivity in an aliquot counted, and the total radioactivity calculated. This was taken to be a true measure of the amount of vitamin B₁₂ excreted in the urine: the proof of this theory and the methods used are described in detail elsewhere (Adams, 1961).

After the first injection of Co-58 vitamin B₁₂ the serum vitamin B₁₂ level was estimated regularly, and when the level fell to about the original pre-injection level a second injection of Co-58 vitamin B₁₂ was given and the cycle repeated. At the end of the period of observation all samples of serum obtained during the study were assayed in two different assay batches by a modification of the methods of Ross (1952) and of Hutner *et al.* (1956), using *Euglena gracilis* 3 strain as the test organism; the results presented here are based on the mean values of these two assays.

Results

Results in six cases are shown in graphical form in Figs. 1-6, and more detailed results from the same patients are set out in Tables I and II. In the figures the amount of vitamin B₁₂ retained is shown in