Summary and Conclusions

Non-spirochaetal infectious jaundice is to be regarded as a general infection in which symptoms of disorganized liver function predominate. These symptoms are due to two main causes: first a maladjustment between the metabolisms of fat and carbohydrate causing acidosis; and secondly an escape of bile into the blood stream causing jaundice, bilirubinuria, a tendency to haemorrhages, etc. Jaundice of skin and conjunctiva is not invariable, and was not present in about 8 per cent. of the present series. Enlargement of the liver is common, occurring in 63 per cent. of cases, and is probably due to a deposit of fat in the liver cells. The spleen was enlarged in 15 per cent. of cases, and 17 per cent. showed albuminuria.

The causative organism or virus is unknown. Guinea-pigs do not appear to be susceptible to the disease. The evidence is in favour of a primary nasopharyngeal infection in some cases. Second attacks are rare, but do occur. The symptomatology differs from that of Weil's disease in degree only. In epidemics, Weil's disease should be excluded as soon as possible.

Every case of "catarrhal" jaundice in children should be isolated for a period of at least four weeks. Any case may be the starting-point of an epidemic. In institutions observation of contacts (particularly with reference to the urine) and quarantine for a similar period should be enforced.

Treatment should be directed principally against the acidosis.

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HUMAN TUBERCULOSIS OF BOVINE ORIGIN
IN STAFFORDSHIRE

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A recent publication by one of us (A. S. G., 1934)¹ on the incidence in England and Scotland of human and bovine tubercle bacilli in tuberculous meningitis included six cases of this disease from Staffordshire. Of these six cases, three proved to be bovine, two human, and one an anomalous dysgonic strain, which is still under investigation. The bovine ratio in this small series prompted a further and more extended inquiry so as to include all forms of human tuberculosis in this county.

During the period from January, 1934, to June, 1935, we have examined bacteriologically six cases of cervical gland, twenty-nine cases of bone and joint, twelve cases of meningeal, two cases of renal, and 230 cases of pulmonary tuberculosis. The original material—aspirated pus, cerebro-spinal fluid, urine—of the non-pulmonary cases was in each instance injected subcutaneously in the thigh of a guinea-pig at the County Bacteriological Laboratory, Stafford.

Each guinea-pig was killed when its inguinal glands were sufficiently enlarged, and was carefully examined to make sure that there were no lesions other than those which were obviously artificially induced. In none of the animals was there any sign or suspicion of spontaneous tuberculosis, which, in fact, has never been observed among the guinea-pigs in this laboratory. One of the inguinal glands adjacent to the seat of injection was excised with sterile precautions and sent to the Field Laboratories, Cambridge, where the tubercle bacilli were cultivated and typed by one of us. The original material of the pulmonary cases was sputum, and from it cultures were obtained in the laboratory at Stafford, either directly with the aid of KOH (5 per cent.), or through the guinea-pig (three instances).

The results in the different forms of tuberculosis are stated separately.

Non-pulmonary Forms of Tuberculosis

Cervical Gland Tuberculosis.—The six cases were in persons aged 1½, 2, 12, 17, 22, and 23 years respectively, of whom three were males and three females. In the child of 12 cervical adenitis had been present since the age of 4 years, and the culture was obtained from a gland which began to enlarge three months ago. In the three older persons the duration of the adenitis ranged from about one up to three years. The tubercle bacilli obtained in culture from each patient exhibited the characters of dysgonic bacilli of the bovine type and were fully virulent for the rabbit. Six rabbits inoculated subcutaneously with these strains died in from twenty-eight to seventy-one days (average 37.9 days) of general tuberculosis typical of infections with bovine tubercle bacilli.

Bone and Joint Tuberculosis.—The twenty-nine cases comprised fourteen of the hip-joint, nine of the spine, and one each of a finger, a rib, a humerus, a sternum, and a knee- and an ankle-joint. The cultures from nineteen cases were culturally of the human type (eighteen eugonic and one dysgonic). The remaining ten cases—namely, five of the fourteen hip-joints, two of the nine spines, and the finger, rib, and humerus—yielded cultures

which culturally were of the bovine type. The dysgonic strains (nine in number, one case having been examined twice) from eight of the latter group were fully virulent for the rabbit. Nine rabbits were inoculated subcutaneously and three intravenously; and all died of severe general tuberculosis in from twenty-two to eighty-three days. The dysgonic strains from the remaining two cases, both of hip-joint disease, exhibited lower virulence for the rabbit than standard bovine strains. The tubercle bacilli from one of these cases, a girl of 18 who had also suffered from lupus of the neck for two years, were cultivated from sinus pus on two occasions with an interval of two months, once directly and once through the guinea-pig. Each of the strains was tested intravenously on a rabbit in a dose of 0.01 mg.; one of the rabbits died in fifty-one days of severe general tuberculosis, the other in eighty-eight days of moderate widely disseminated tuberculosis. The two strains were also tested subcutaneously, one on two rabbits, the other on one. The three rabbits died or were killed eighty-seven to 126 days later and showed large caseous adjacent glands and generalized tuberculosis, slight in two and moderate in one; the kidneys in one rabbit contained projecting nodules and the epiphyseal ends of the femurs of another were extensively caseous. The second case yielding an attenuated strain was in a girl of 11 who had had hip-joint disease for nine years. Three rabbits were inoculated, two intravenously (doses 0.01 and 0.001 mg.) and one subcutaneously (dose 5 mg.); they died or were killed in 52, 100, and 100 days respectively and showed generalized tuberculosis, which, however, was of only moderate severity. An indication that the bacilli were not of full virulence was given by the result in the guinea-pig inoculated with the pus from the hip; this animal showed very limited disease after two months. Such strains of reduced virulence are not infrequently encountered, especially in human skin tuberculosis, although they also occur from time to time in chronic tuberculous affections of bones, joints, lungs, peritoneum, and glands.

Table showing the Age Incidence of the Human and Bovine Types of Tubercle Bacilli in the Bone and Joint Cases

	Number	Human	Bovine
Under 5 years	5	3	2
5 to 9 "	10	8	2
10 to 15 "	4	2	2
Over 15 "	10	6	4*
	29	19	10

* One of these cases was in a farm labourer, aged 62, who pricked his right ring-finger with a thorn some months before tuberculous tenosynovitis supervened. A bulk sample of milk of his employer's herd was positive in September, 1930, and two cows were slaughtered.

Tuberculous Meningitis.—Twelve cases were examined, and the cultures were derived in each instance from cerebro-spinal fluid through the guinea-pig. From seven of the cases the strains exhibited the characters of the eugonic human type of tubercle bacillus. From the remaining five the strains were typically dysgonic bovine culturally and were fully virulent for the rabbit. Six rabbits were inoculated, four intravenously (doses, 0.01 and 0.001 mg.) and two subcutaneously, each with the growth from one primary culture; they died in 17, 17, 26, 48, 60, and 71 days respectively of typical severe general tuberculosis. For comparison one of the eugonic strains was tested intravenously on a rabbit in a dose of 0.1 mg. of culture; the rabbit was killed ninety-four days later, and showed only slight tuberculosis of the lungs and kidneys. The following table shows the age incidence of the two types of bacilli in the meningitis cases.

	Number	Human	Bovine
Under 5 years	7	3	4
12 and over	5	4	1*
	12	7	5

* A woman aged 23 years.

Of the patients six were female and six were male. Two females and three males were infected with bovine bacilli.

Renal Tuberculosis.—The two cases of this form of the disease, one in a woman of 29 and one in a man of 25 years, yielded cultures of human type.

Pulmonary Tuberculosis

Specimens of sputum were received from 263 persons suffering from pulmonary tuberculosis in three institutions. As previously stated the sputum was treated with KOH for half an hour at 37° C. and then sown both upon plain egg and upon 5 per cent. glycerin egg. Plain egg was used in every instance because tubercle bacilli of bovine type usually either do not grow or grow scantily on the glycerinated medium. Pure cultures of tubercle bacilli were obtained in 230 of the cases. In thirty-one cases the cultures failed owing to contamination and repeat specimens were unobtainable, either because the patients had died or had left the district. In two cases where the cultures failed owing to contamination repeated examination failed to reveal tubercle bacilli. Of the 230 strains of tubercle bacilli 227 were culturally of eugonic human type, one was dysgonic human, and two were dysgonic bovine.

Strains of eugonic human type were not tested on animals, the classification being based entirely on growth characters on egg and glycerinated potato. The dysgonic human strain, which grew well on egg and with difficulty on glycerinated potato, was tested on a rabbit intravenously and on a guinea-pig subcutaneously, the dose in each instance being 0.1 mg. The rabbit was killed 104 days later and showed only a moderate amount of tuberculosis in the lungs and a few lesions in the kidneys. The guinea-pig was killed, when ill, ninety-two days after inoculation and showed general tuberculosis of mild type.

Particulars of the Two Bovine Cases

Case 1.—Male, 20 years, errand boy, then in engineering works and afterwards occasional outside farm worker; in sanatorium from October, 1932, to August, 1934. The patient had measles at 11 and quinsy at 13. He had not drunk much raw milk and there was no history of cervical adenitis. On admission the left upper lobe and apex of left lower lobe were infiltrated. Later the signs became rather more extensive on the left side and the right upper lobe was also involved. He died at home from severe haemoptysis in October, 1934, about two years and nine months after the beginning of clinical pulmonary tuberculosis. The parents and five brothers and sisters were healthy, and there was no family history of tuberculosis. A culture obtained directly from the sputum was dysgonic, and, in a dose of 10 mg. subcutaneously, caused severe general tuberculosis in a rabbit, which died in fifty-six days. Only one specimen of sputum was examined, the patient dying before the type of bacillus had been ascertained.

Case 2.—Male, 26 years, miner, admitted to sanatorium in 1926. As a child was rickety, with much deformity of chest. He had pneumonia when 3 years old, and had been ill intermittently ever since childhood. There was no history of glandular tuberculosis. On admission there was advanced disease of both lungs, more on the left side, with much malformation of chest—scoliosis and lordosis—and other

rickety deformities. He is mentally dull. During the years he has been in the sanatorium he has not changed much, but the disease is slowly progressing and the prognosis is unfavourable; sputum 2 to 3 oz. daily. There is no family history of tuberculosis. For eight years he has drunk half a pint of raw milk daily. Cultures of tubercle bacilli were obtained from the sputum on three occasions, once in August and twice in November, 1934. The three strains were dysgonic (Class 2), and proved highly virulent for the rabbit. Each strain was injected intravenously into a rabbit, the doses ranging from 0.01 mg. to less than 0.001 mg.; the rabbits died in 21, 34, and 61 days of typical severe general tuberculosis.

Milk Supply

Inquiries were made into the milk supply of all the non-pulmonary bovine cases. In many instances biological tests of bulk samples of the milk from the farms supplying the households had been made prior to our investigations.

These tests were positive in connexion with eleven of the cases, four of which were in adolescents or adults aged 17, 20, 20, and 23 years respectively, and seven were in children whose ages ranged from 18 months to 3½ years. In one of the latter instances the sample which was positive was taken five to six months before the child, aged 18 months, died of tuberculous meningitis. In another, several bulk samples were positive and six cows were slaughtered during a period of two years before the patient, a boy aged 2½ years, died of tuberculous meningitis. In a further instance, a girl of 2 with cervical adenitis, the milk was positive on several occasions and several cows were slaughtered. Among adults also there appears to have been direct relationship between the milk supply and the tuberculosis. For example, the patient aged 23, a woman who was in the habit of drinking milk in the raw state and who died of bovine tuberculous meningitis, obtained the milk from a supply which had given numerous positive samples. We may mention that for Staffordshire as a whole the percentage of bulk milk samples containing tubercle bacilli during the period in question was 8.48.

Summary

We have determined the types of tubercle bacilli in forty-nine cases of non-pulmonary tuberculosis derived from the county of Stafford. All the cases (six in number) of cervical gland tuberculosis, five of twelve cases of tuberculous meningitis, and ten of twenty-nine cases of bone and joint tuberculosis, yielded cultures of bovine tubercle bacilli. The remainder—namely, seven cases of tuberculous meningitis and nineteen of bone and joint and two of renal tuberculosis—yielded cultures of human tubercle bacilli. These results show that in Staffordshire the percentage frequency of bovine infections in non-pulmonary tuberculosis is somewhat similar to that found in some parts of Scotland. In human pulmonary disease in Staffordshire, on the other hand, the incidence of bovine infections does not at all approach the high percentage of the Scottish figures. In North-East Scotland, comprising the three counties of Aberdeen, Banff, and Moray, the percentage of pulmonary bovine infections in a preliminary series (1935)¹ was 17 as against rather less than 5 for the rest of Scotland, whereas for Staffordshire the percentage of bovine pulmonary infections revealed by this investigation was under 1. Although it is possible that some of the cases from which cultures of tubercle bacilli were not obtained may have been bovine infections, it is unlikely that there could have been so many as would raise the incidence of pulmonary bovine infections in Staffordshire to the level of the Scottish figures. The Staffordshire figures for bovine infections in human lung tuberculosis are more in consonance with the previous figures for England than with the Scottish figures.

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GLYCOSURIA OF "LAG STORAGE" TYPE: AN EXPLANATION

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Since the "lag" type of blood sugar curve was first described by MacLean no further attempt has been made to assess or explain it. To judge from the numbers of such curves in my own experience hundreds must have been observed, but the true significance has not been definitely established. Certainly life assurance companies do not accept the condition with the confidence in which they now regard another type of non-diabetic glycosuria—renal, or orthoglycaemic, glycosuria. However, I have observed it so often after gastro-enterostomy and in duodenal ulcer that I have come to the conclusion that it is to be explained entirely by rapid intestinal absorption of sugar, and does not point to any abnormality in carbohydrate metabolism.

The "Lag Storage" Curve

The characteristic features are indicated in the chart, which shows the results obtained a month after gastro-enterostomy in a young woman who was known to be aglycosuric before operation. Before 50 grams glucose by mouth and at half-hourly intervals afterwards, the blood sugar concentrations were 103, 260, 213, 100, 77 mg. per cent. Glycosuria was absent except at the half and the one-hour urinary voiding, when some 2 to 3 per cent. was present. This is a curve typical of the condition. The fasting level is normal; a rapid hyperglycaemia between 0.2 and 0.3 per cent. occurs at the first half-hour and quickly returns to the normal in one and a half to two hours. In other curves the blood sugar may be higher at one than at half an hour, but, even so, a rapid and complete return to normal in two hours makes the diagnosis conclusive. Temporary glycosuria occurs when the renal threshold is exceeded, and if the renal threshold is low, which I have noted in several cases, glycosuria is persistent throughout the curve.

N.B.—Only arterial blood shows it.

A few other observations should be noted. If venous instead of capillary (arterial) blood be analysed, this type of curve will seldom be noted. This explains the rarity with which the condition has been noticed in America, where, until recently, venous blood has mostly been used in blood sugar curves. The rise in the blood sugar, say from 0.1 to 0.3 per cent. in half an hour, is much quicker than is seen in the typical "diabetic" curve.

If these patients are also tested with 50 grams laevulose, the curves are entirely normal. For example, the patient whose blood sugar is shown in the chart gave the following result: 116, 139, 115, 109, 101 mg. per cent., and excreted a slight trace of laevulose by Selivanoff's test. The absorption of laevulose from the intestine is so much slower than glucose that a flat laevulose curve is to be expected. In one young man, however, the blood sugar rose half an hour after laevulose to 0.172 per cent. (glucose, 0.25 per cent.), but returned rapidly to normal, the latter quite different from either the diabetic or liver deficiency response to laevulose.

If several curves are carried out on these individuals within short intervals considerable variations in hyper-