Summary

A case of perforation of the small intestine resulting from one of three argentaffin tumours of the ileum is described. Treatment was by excision of all three, restoration of the continuity of the gut, and closure of the abdomen without drainage after liberal application of sulphanilamide powder to the operation sites. The patient recovered uneventfully.

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EFFECTS OF HYPERTHERMIA AND ANTIBACTERIAL AGENTS ON TUBERCLE BACILLI

BY

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Since their first isolation, it has been recognized that the mammalian types of tubercle bacilli will multiply in artificial culture only within a narrow temperature range. The human type is more fastidious than the bovine in this respect, a property which has been correlated with the predilection of the human type for parasitizing those mammals which have relatively low body temperatures. Fever therapy, which has proved useful in general paralysis and in certain gonococcal diseases, has had limited trials in tuberculosis of man and experimental animals. For example, Kling and Rubin (1936) induced pyrexia in tuberculous guinea-pigs by means of periods of short-wave treatment lasting only ten minutes. Duncan and Mariette (1937) treated tuberculous guinea-pigs in a fever cabinet for periods of four to five hours once weekly for 10 weeks. They also treated patients with weekly periods of fever lasting one to three hours. No definite benefit was observed in these trials, but the short or infrequent periods of fever employed could hardly have been expected to have a direct effect on the tubercle bacilli. Some benefit may have been anticipated by the experimenters, however, from the effects of the fever on the defences of the host.

The present work initiates an investigation into the part which hyperthermia may usefully play as an adjuvant to the treatment of tuberculosis with streptomycin and chemotherapy, whose present limitations are becoming increasingly evident. The chief defects of streptomycin treatment are the restrictions imposed on dosage by toxicity, the frequent appearance of resistant strains during its course, and the failure of response of those lesions into which penetration of the antibiotic is difficult. In such lesions it seems that the appearance of resistant mutants is facilitated owing to the exposure of the bacilli to sublethal concentrations of streptomycin.

The experiments described below show that the sensitivity of tubercle bacilli to streptomycin may be considerably enhanced by cultivating the organisms at a temperature above the optimum. The temperature chosen was 40° C. (104° F.), which is one readily attained in fever therapy. The strains examined were all of the human type (judged by cultural characteristics). Para-aminosalicylic acid and a thiosemicarbazone (*p*-acetylaminobenzaldehyde thiosemicarbazone), which are the most promising of the newer synthetic drugs, were also investigated, while mercuric chloride provided the contrast of a simple disinfectant.

Experimental Methods

Sensitivity titrations at 40° C. ($\pm 0.2^\circ$ C.) were incubated in a large insulated water-bath (55 by 40 cm.) fitted with a "sunvic" unit. Owing to the temperature gradient between the centre and walls of the bath, the tubes of medium were not all at the same temperature, but by lagging the walls and avoiding the periphery of the bath the range was limited to 39.8°–40° C. A bath of the same type with a temperature range of 36.8°–37° C. was used for control titrations. Similar results were obtained, however, when controls were incubated in a 37° C. air incubator in which the temperature of the medium reached 36.5°–37° C.

The culture medium employed, derived from Dubos's work, had the following composition: KH_2PO_4 1 g., Na_2HPO_4 3.1 g., sodium citrate 1.5 g., MgSO_4 0.6 g., asparagin 2 g., "tween" 80 0.5 ml., glass-distilled water 1 litre. It was dispensed in 2.5-ml. amounts in $\frac{1}{4}$ -oz. (7-ml.) bijou screw-capped bottles and autoclaved at 10 lb. (0.7 kg. per cm.²) pressure for 15 minutes. Before inoculation, 0.1 ml. of a 9% solution of bovine albumin was added aseptically to each bottle. The thiosemicarbazone was autoclaved, but the *p*-aminosalicylic acid (sodium salt) and mercuric chloride were sterilized by heating 1% and 0.1% solutions, respectively, in a boiling water-bath for 15 minutes.

The strains of tubercle bacilli investigated had been recently isolated from cases of pulmonary tuberculosis. Before use they had undergone three weekly subcultures in Dubos's medium after their primary isolation on solid medium. The grown cultures were sometimes stored at 4° C. for short periods until required. One drop (approximately 0.03 ml.) of such a culture was used to inoculate each tube of a titration. The strains whose streptomycin sensitivity was studied were chosen from a group somewhat more resistant than the average, being inhibited (at 37° C.) by concentrations ranging from 0.25 to 4 units per ml.

Readings were made by comparing the turbidity of cultures with barium sulphate standards in bijou bottles. The amount of growth was recorded by a numeral representing the amount of barium chloride in mg. per 100 ml. giving a similar opacity in the presence of an excess of 1% sulphuric acid. Opacities less than 0.6 were recorded as "trace" and above 40 were not distinguished from 40. The intervals between standard tubes were 100%, but intermediate values were estimated when possible.

Results

Not all of the strains of tubercle bacilli tested gave sufficient growth at 40° C. to permit satisfactory titrations. Of 40 strains examined on this point, 10 developed opacities of less than 2.5 after seven days' incubation

at 40° C. Most experiments were performed on strains growing fairly well at 40° C., but those on strains growing less well gave similar results. Stocks stored for some weeks at 4° C. grew less readily at 40° C.

The first part of the accompanying Table records the streptomycin sensitivity of one strain, determined at 37° C. and at 40° C. The titration at 40° C. was transferred, after the period stated, to 37° C. to find out whether the effect of hyperthermia was permanent. In

Discussion

On two occasions during the examination of a few strains growing poorly at 40° C. heavy growth was observed in a single tube of a sensitivity titration (not the control tube). This finding suggests that growth which appears at 40° C. results from the activity of only a fraction of the inoculum. This explanation is supported by the failure of some stock strains of tubercle bacilli

Sensitivity to Antibacterial Substances of Tubercle Bacilli (Human Type) Grown at (a) 37° C. and (b) 40° C. with Subsequent Transfer to 37° C.

Antibacterial Substance	Titration	Temperature of Incubation	Period of Incubation	*Degree of Growth with Given Concentration of: (i) Streptomycin in Units per ml.								
				4	2	1	0.5	0.25	0.12	0.06	0.03	Nil
Streptomycin	(a)	37° C.	7 days	0	0	0	1.2	10	15	15	15	15
	(b)	40° C.	7 "	0	0	0	0	0	0	0	1.2	10
	(a)	37° C.	Further 7 days	0	0	1.2	10	15	20	30	30	30
	(b)	37° C.	7 days after transfer	0	0	0	0	0	5	15	20	20
(ii) Thiosemicarbazone in mg./100 ml.												
Thiosemicarbazone				1	0.5	0.25	0.125	0.062	0.031	0.016	0.008	Nil
	(a)	37° C.	7 days	0	0	0	0.6	1.2	0.6	10	1.2	20
	(b)	40° C.	7 "	0	0	0	0	0	0	Trace	0	10
	(a)	37° C.	Further 7 days	0.6	Trace	0.6	5	10	0.6	20	10	40
	(b)	40° C.	" 7 "	0	0	Trace	0.6	Trace	0.6	0.6	Trace	20
	(a)	37° C.	" 7 "	1.2	2.5	5	10	15	10	20	15	40
	(b)	37° C.	7 days after transfer	0	0	0.6	2.5	Trace	2.5	1.2	0.6	30
(iii) Mercuric chloride in mg./100 ml.												
Mercuric chloride				6.4	3.2	1.6	0.8	0.4	0.2	0.1	0.05	Nil
	(a)	37° C.	7 days	0	0	0	5	10	10	10	10	10
	(b)	40° C.	7 "	0	0	0	Trace	0.6	1.2	2.5	5	5
	(a)	37° C.	Further 7 days	0	0	0	20	30	30	30	30	30
	(b)	37° C.	7 days after transfer	0	0	0	5	10	10	10	20	20

* Recorded in terms of barium sulphate standards (see text). Traces of growth (<0.6) denoted by "trace."

this example the sensitivity to streptomycin was increased 16 times by cultivation at 40° C., and the increase largely persisted after transfer to 37° C. Twelve other strains that were tested against streptomycin increased in sensitivity between 8 and 32 times at 40° C., the effect being somewhat greater with the strains growing poorly at this temperature.

The effect of hyperthermia on the sensitivity of tubercle bacilli to *p*-aminosalicylic acid was the same as on streptomycin sensitivity, so does not need to be recorded separately. Concentrations from 2 mg. to 0.002 mg. per 100 ml. were chosen according to a preliminary estimate of sensitivity. Strains of high resistance, derived from patients who had undergone treatment with the drug, increased in sensitivity at 40° C.

In titrations of sensitivity to thiosemicarbazone there was often difficulty in determining the end-point. This was due to the common finding of small amounts of growth in several successive twofold dilutions of drug and also to what appeared to be the frequent occurrence of variant bacilli of high resistance. However, those titrations with definite end-points did show an increase in sensitivity at 40° C. as with streptomycin and *p*-aminosalicylic acid. A typical set of titrations of sensitivity to thiosemicarbazone is recorded in the second part of the Table. Incubation at 40° C. was continued for 14 days before transferring to 37° C., but both 7- and 14-day readings are given.

When growth was sufficient for a satisfactory titration, hyperthermia had little effect on sensitivity to mercuric chloride. Although the end-points of titrations at 40° C. showed little or no alteration from those at 37° C., growth was impaired to varying degrees. Representative titrations are given in the last part of the Table.

to give consistently successful subcultures at 40° C. Further work is required to clarify the mechanism responsible for the experimental findings, but as a working hypothesis it appears reasonable to suppose that the great increase of sensitivity to streptomycin and *p*-aminosalicylic acid obtained by cultivating at 40° C. is due to the requirement for growth of the presence of variants insensitive both to the drug and to the higher temperature. Such variants would be much rarer than bacilli resistant to the drug alone.

The sensitivity to streptomycin or *p*-aminosalicylic acid of a strain examined by the technique described above is only an expression of the incidence in the inoculum of resistant variants whose degree of resistance is in inverse ratio to their frequency. The reduction in the number of viable resistants due to cultivation at 40° C. is therefore reflected in the increase in sensitivity. With thiosemicarbazone, the degree of resistance and the infrequency of incidence of resistant variants do not appear to be correlated in this way. Consequently the effect of cultivation at 40° C. may sometimes be partly obscured by the irregular appearance of variants with high resistance to the drug. Similar reasoning suggests that the small increase in sensitivity to mercuric chloride observed in titrations at 40° C. is due to all the bacilli of a strain having approximately the same susceptibility to the disinfectant. This homogeneous reaction is also shown by different strains, all of those tested at 37° C. being inhibited by the same concentration of mercuric chloride.

If the conditions of these experiments at 40° C. could be paralleled *in vivo* the effectiveness of treatment with the therapeutic agents examined might be expected to show a considerable improvement. It is not safe to

maintain a temperature of 40° C. (104° F.) in patients for long periods, but since it is customary to administer streptomycin by a single dose daily it might be practicable to enhance the effect of the streptomycin by inducing fever during the period of maximal concentration in the tissues. Unfortunately, the effects on tubercle bacilli of short exposures to hyperthermia and streptomycin cannot be conveniently studied *in vitro* owing to the difficulty of reproducing the changing streptomycin concentrations that occur in a treated patient.

Smith and Vollum (1950) observed that certain cases of tuberculous meningitis benefited by the administration of tuberculin intrathecally during treatment with streptomycin. Their records show that a febrile reaction was provoked by the tuberculin injections, and it is possible that the beneficial effect of these injections was due, in whole or part, to the combination of the fever they produced and streptomycin. As injections of tuberculin are hazardous, it is important to ascertain whether they can be replaced by fever therapy, which may be applied in a controllable form.

It is hoped that animal experiments will provide further evidence of the synergism of hyperthermia and streptomycin and *p*-aminosalicylic acid. Such experiments should not, however, preclude clinical trial, because the reaction of man to infection by the tubercle bacillus cannot be exactly reproduced in any animal. As a direct action on the organism is aimed at, the induction of a temperature of at least 104° F. (40° C.) should be attempted; it should be reached approximately one hour after the injection of streptomycin and be maintained for four to six hours. The number of such courses would vary with the tolerance of the patient, but it is probable that they would best be given on successive days. *Para*-aminosalicylic acid could be administered at the same time.

Summary

About 25% of strains of *Myco. tuberculosis* (human type) grew very poorly in Dubos's medium at 40° C. The growth of the remainder was slightly or moderately impaired.

The sensitivity of strains growing sufficiently well for testing at 40° C. was considerably increased to streptomycin, *p*-aminosalicylic acid, and often to thiosemicarbazone, but not to mercuric chloride.

Reasons are advanced for trying a combination of hyperthermia with streptomycin and *p*-aminosalicylic acid treatment in tuberculosis of man caused by the human type of bacillus.

I am indebted to Dr. B. A. D. Stocker for a discussion of the mechanism of the phenomena recorded, and to Dr. G. S. Wilson and Dr. Scott Thomson for improvements in the presentation.

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The whole undergraduate population of the Queen's University, Belfast, was examined radiologically once in the academic year 1950-1, states the third annual report of the student health medical officer. Seventeen cases of active tuberculosis were noted among the 2,368 students, and eight of these cases had been in normal health a year previously. No reason for their breakdown in health could be found in their mode or conditions of life, and the source of their infection remained unknown.

AN UNUSUAL METHOD OF TREATING HYDROCEPHALY

BY

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Nowadays the treatment of hydrocephalus is more or less standardized: the head is collapsed per vaginam either by puncturing it with a sharp instrument, with or without drainage through a cannula, or by the passage of a hollow instrument up the spinal canal into the brain.

The following case is presented because the above methods failed when attempted per vaginam. The method employed was puncture of the head and drainage through a cannula, but it was carried out through the maternal abdominal wall. This method is not claimed as original. It is mentioned on several occasions in the literature, but no details are given. It is this absence of detail that has prompted me to publish the following case.

Clinical History

A primigravida, aged 31 and married eight years, first attended the antenatal clinic on September 20, 1949. She was then 22 weeks pregnant. The uterus corresponded in size with the duration of amenorrhoea. No abnormality was detected. Her blood pressure was 110/60; her urine was clear.

On November 17, when she was 30 weeks pregnant, the uterus was the size of a 34-weeks pregnancy. The presenting part was thought to be a breech, but the head could not be identified in the fundus. A radiograph showed a single foetus, of about seven months' maturity, presenting as a breech. The head was extended and appeared slightly enlarged. On November 19 external cephalic version was attempted, but was unsuccessful. It was then decided that an abnormal foetus with hydrocephaly was likely, and that a further x-ray examination should be made in three weeks, by which time there should be no doubt about the diagnosis.

At 9 a.m. on December 8, when 33 weeks pregnant, the patient was admitted to hospital in early labour. The membranes had just ruptured and there had been a sudden gush of liquor amnii. The findings on abdominal palpation were difficult to interpret, but a large soft swelling could be felt in the fundus, and this was thought to be a hydrocephalic head. The foetal heart rate was 120 per minute. On rectal examination the presenting part was thought to be a breech, in mid-cavity, with the os dilated to one to two fingerbreadths. A radiograph was requested, but the x-ray plant was under repair and could not be used. Uterine contractions were quite strong and were occurring every seven minutes.

At 1 p.m., on vaginal examination, a complete breech was felt, which had descended as far as the ischial spines, and the os was dilated to four fingerbreadths. By 4 p.m. the contractions were much weaker and no advance had been made. In an effort to stimulate contractions a course of stilboestrol was given—10 mg. quarter-hourly for 12 doses. The pains became stronger again about 10 p.m., but after two hours of these stronger pains there was still no progress.

At 12 midnight an examination under general anaesthesia—gas, oxygen, and ether—was carried out. The large soft swelling in the fundus was now definitely identified as a hydrocephalic head. No further dilatation of the cervix had taken place. Since the progress of labour had been arrested, the anterior leg was brought down so that the half-breech could act as a cervical dilator. At 1 a.m. she