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# Oral humatin (paromomycin) in chronic enteric carriers

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## INTRODUCTION

From the time that Koch in 1902 first drew attention to the importance of the typhoid patient or the typhoid convalescent as the most serious source of spread of enteric fever, and von Drigalski (1904) traced the course of the condition from the convalescent to the chronic carrier state, numerous attempts have been made by both surgical and non-surgical procedures to eradicate the possibility of infection from this source. Logically this can only be achieved by preventing the carrier condition by the complete cure of the original infection or by the complete eradication of the carrier condition if it develops. Early attempts to achieve the latter aim—the former is still beyond us—have been reviewed by Sacquépée (1910), Ledingham & Arkwright (1912), Gay (1918), and more recently by Browning, Coulthard, Cruickshank, Guthrie & Smith (1933). Apart from the rare urinary carrier with a persistent focus of infection which may be amenable to surgical treatment, there is only one group of carriers, the chronic biliary, in which any measure of success has resulted from these efforts. There is little doubt that in certain cases belonging to this group the operation of cholecystectomy is accompanied by a high proportion of permanent cures, provided certain criteria are fulfilled in selecting the case for surgery (Haaland & Haaland, 1927; Whipple, 1929; Bigelow & Anderson, 1933; Senftner & Coughlin, 1933; Coller & Forsbeck, 1937 and Littman, Vaichulis & Ivy, 1949).

In mental hospitals the problem of the enteric carrier is a particularly important one. The low standard of personal hygiene so frequently exhibited by patients suffering from certain types of mental disease greatly increases the risk of infection spreading from the carriers, of which an undue proportion are to be found in most of the larger institutions caring for the long-term patients. In the past several serious outbreaks of typhoid fever involving not only the staff and the patients of the institution itself but extending beyond this barrier have been undoubtedly due to these carriers. In spite of the spectacular advances in the treatment of mental diseases in their early stages the elderly long-term patient in the large institutions who is an enteric carrier is likely to remain a problem for some time to come. Confronted with the legal difficulties associated with the performance of cholecystectomy on certified patients, it would seem, in spite of the disappointing results of all chemotherapeutic measures which have been so far advocated, important that any anti-bacterial agent to which the typhoid and paratyphoid bacilli are sensitive should be fully investigated.

Humatin (paromomycin), a white, amorphous, basic water-soluble antibiotic derived from *Streptomyces rimosus* forma *paromomycinus*, has been shown experimentally to posses marked antibacterial action against the enteric group of organisms (Coffey, Anderson, Fisher, Galbraith, Hillegas, Kohberger, Thompson, Weston & Ehrlich, 1959), and to be of value in the treatment of acute salmonella infections (McMath & Hussain, 1959). Moreover, when the drug is administered orally little of the drug appears to be absorbed into the bloodstream; urinary recovery is low but the faecal level, on the other hand, is high (Coffey *et al.* 1959), thus permitting a high concentration to be maintained within the intestine and at the same time rendering possible toxic effects of a systemic nature less likely. Although little work has been carried out as yet in the treatment of the chronic enteric carrier state by this drug certain unpublished experimental work suggested that in certain groups of enteric carriers it was of definite value. It was therefore decided to undertake a clinical trial to determine its effect on the progress of the carrier state in a group of long standing enteric carriers.

## METHODS

### *Design and conduct of the trial*

#### *Selection of patients*

All patients selected for inclusion in this trial had been under continuous supervision as in-patients, and were proven enteric carriers of at least 2 years standing. According to the frequency with which the specific organisms had been isolated from the faeces on routine monthly examinations they were placed in one of two categories, the first, A, being those patients in whom at least 90 % of the specimens submitted to the laboratory proved positive for salmonella on bacteriological examination, whilst the second category, B, contained the remaining patients in whom the excretory pattern of salmonella organisms was of a more intermittent nature. Both groups received identical treatment. Urinary, as well as faecal, carriers of enteric organisms were included in the trial.

#### *Clinical control*

A careful clinical and pathological examination of both groups was made prior to and on completion of the trial. In patients in whom the clinical and mental condition permitted it cholecystograms were carried out in order to obtain some measure of the state of gall-bladder function. Pre- and post-trial blood samples were taken from all patients, and haemoglobin level, packed cell volume, blood sedimentation rate, white cell count, and differential cell count determined. A urine specimen from each patient was examined microscopically, chemically and bacteriologically.

#### *Serological control*

Serum Vi, H and O agglutination titres of the patients were determined, using standard suspensions of *Salmonella typhi* and *Salm. paratyphi B*; the serum specimens being divided into two halves one of which was submitted to an independent

laboratory for checking. In each case serum was taken prior to administration of Humatin, and a further specimen some 6 weeks later.

*Bacteriological control*

Daily faecal specimens were taken for the first 14 days from all patients included in the trial, after which weekly specimens were taken for 6 weeks, and monthly specimens for 2 months; had these specimens remained negative for enteric organisms a further sixteen monthly specimens followed by a single biliary specimen would have been taken for bacteriological examination.

In order to minimize the possibility of cross-contamination the stool was passed into a commode pan lined with cloth onto an inner lining of waxed paper, a sample of the freshly passed stool then being placed into special containers supplied by the laboratory, it was then immediately forwarded for examination.

On receipt of the stool specimen at the laboratory it was emulsified in saline and direct platings were made on bismuth-sulphite agar and on deoxycholate-citrate agar. Each specimen was also inoculated into selenite-F broth and after 24 hr incubation at 37° C. in this enrichment medium subculture platings were made on to bismuth-sulphite agar and deoxycholate-citrate agar. In examining the plate cultures after 24 and 48 hr. incubation previous experience of the particular patient's specimens was helpful in selecting colonies for provisional identification, but all typhoid or paratyphoid-like colonies were fully examined biochemically and serologically to confirm their identity.

Although every care was taken to ensure that there was no mixing of specimens it was considered that the phage-typing of the typhoid and paratyphoid organisms isolated would provide a useful check on this. There was also the possibility of some unexpected disclosures following the treatment with Humatin. Dr A. Bernstein of the Central Enteric Reference Laboratory and Bureau kindly agreed to determine, where possible, the phage-type of the various organisms isolated.

The *in vitro* sensitivity of the various strains isolated, before and after the trials, to humatin partial sulphate (75%), in concentrations of 5, 10 and 20 $\mu$g/ml. respectively were also determined.

*Criteria of cure*

Considerable variation in criteria of cure of the enteric carrier state is seen in the published literature. In the present trial it was decided that patients should be accepted as being cured of their carrier state if they fulfilled the following criterion:

*Bacteriological*—daily specimens of excreta to be negative for 14 days, weekly specimens negative for 6 weeks, and monthly specimens for 16 months, together with a single negative bile specimen examined at the end of this period.

*Dosages*

For clinical administration the Humatin was supplied in the form of a syrup containing 250 mg. Humatin base per ml. Females were given 3 g. per day of

Humatin base in three divided doses, males 4 g. per day in four divided doses, the course of therapy lasting 6 days. This dosage being within the average of 2–6 g. Humatin base daily administered in four divided doses and continued for a period of 6 days that is recommended.

## CLINICAL MATERIAL

Twenty-seven chronic mental patients were included in the trial, twenty-four females, and three males. Their ages ranged from 48 to 82 years. The first group of patients A consisted of those patients from whom the specific enteric organisms had been regularly isolated, and included three females excreting *Salm. typhi*, and seven females excreting *Salm. paratyphi B*. The second group B included four females and three males irregularly excreting *Salm. typhi*, and ten females excreting *Salm. paratyphi B*.

All cases included in the trial had been classified as chronic enteric carriers, but largely as a result of their mental state it proved impossible to obtain any history regarding the date and incidence of possible primary attacks of enteric fever. In each instance the recorded minimal duration of the carrier state is taken as that period from the first proven isolation of the specific organism. In several cases the actual duration of the carrier state is probably considerably longer than that actually recorded.

Apart from the segregation of male and female patients in different buildings patients within the two groups lived in close proximity, sharing communal feeding arrangements, and thereby increasing the possibility of cross-infection within the group.

The underlying mental condition necessitating confinement to a mental hospital is shown in Table 1. Five of the patients were confined to bed, the remainder fully ambulant. Nineteen (67%), all females, showed disordered gall-bladder function as evidenced clinically by a history of gall-bladder pain, or intermittent attacks of obstructive jaundice; or radiologically by lack of dye concentration on cholecystography, or the presence of opaque stones in the gall-bladder.

The great majority of patients in both groups had, in previous years, been subject to attempts to sterilize their biliary tract by non-surgical means, notably by the use of chloromycetin, and penicillin and benemid with singularly unsuccessful results. In none of these cases had cholecystectomy been attempted.

The pre-trial excretory pattern of enteric organisms for the previous 4 years is shown in the accompanying table (Table 2). It will be seen that the cases fall readily into the two groups A and B, mentioned earlier. All may be classified as chronic enteric carriers with probably the gall-bladder and biliary tract serving as the persistent focus of infection in the majority of cases. In the pre-trial investigation two patients (cases 7 and 8) were found to be regularly excreting *Salm. paratyphi B* in the urine in addition to excretion of the same organism in the faeces.

Table 1

| No. | Case | Age | Minimal duration of carrier state (years) | Clinical diagnosis | Clinical state |
|---|---|---|---|---|---|
| | | | Group A. Regular excretors | | |
| *Salm. typhi* (females) | | | | | |
| 1 | E.B. | 67 | 15 | Confusional insanity | Ambulant |
| 2 | F.C. | 61 | 13 | Secondary dementia | Ambulant |
| 3 | E.M. | 48 | 6 | Chronic mania | Ambulant |
| *Salm. paratyphi B* (females) | | | | | |
| 4 | F.B. | 75 | 15 | Senile dementia | Ambulant |
| 5 | M.F. | 84 | 14 | Mania, epilepsy | Bed-ridden |
| 6 | W.H. | 63 | 5 | Melancholia | Ambulant |
| 7 | A.K.* | 71 | 5 | Confusional insanity | Ambulant |
| 8 | A.L.* | 57 | 15 | Chronic mania | Mute, dement |
| 9 | R.L. | 62 | 6 | Dementia | Ambulant |
| 10 | A.P. | 66 | 16 | Schizophrenia | Bed-ridden |
| | | | Group B. Intermittent excretors | | |
| *Salm. typhi* (females) | | | | | |
| 11 | E.C. | 64 | 15 | Mania | Ambulant |
| 12 | E.H. | 72 | 13 | Dementia | Ambulant |
| 13 | E.S. | 58 | 18 | Schizophrenia | Ambulant |
| 14 | R.W. | 60 | 6 | Manic depressive | Ambulant |
| *Salm. typhi* (males) | | | | | |
| 15 | J.F. | 61 | 17 | Epilepsy | Ambulant |
| 16 | F.M. | 50 | 9 | Primary dementia | Ambulant |
| 17 | H.R. | 70 | 2 | Confusional insanity | Emaciated |
| *Salm. paratyphi B* (females) | | | | | |
| 18 | A.E. | 82 | 15 | Melancholia | Ambulant |
| 19 | N.B. | 44 | 15 | Schizophrenia | Ambulant |
| 20 | E.B. | 65 | 8 | Manic depressive | Ambulant |
| 21 | E.C. | 79 | 7 | Senile dementia | Feeble |
| 22 | T.D. | 62 | 14 | Confusional insanity | Ambulant |
| 23 | M.G. | 56 | 5 | Schizophrenia | Ambulant |
| 24 | F.H. | 69 | 7 | Mania | Ambulant |
| 25 | M.I. | 73 | 10 | Primary dementia | Bed-ridden |
| 26 | S.S. | 76 | 7 | Dementia | Ambulant |
| 27 | J.W. | 76 | 7 | Schizophrenia | Ambulant |

* Urinary as well as faecal excretor of Salmonella.

## RESULTS

The results of the bacteriological examination of faecal specimens for enteric organisms during and after the trial are presented in Table 3. It is seen that after the first day of treatment no enteric organisms could be isolated from the faecal specimens during the period in which the patients were receiving oral Humatin. On the day following cessation of therapy six of the patients in group A were

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Table 2. *Excretion of enteric bacilli prior to April* 1959

| No. | Case | Year ... 1955 | 1956 | 1957 | 1958 | 1959 |
|---|---|---|---|---|---|---|
| | | Result of monthly faecal examinations | | | | |
| | | **Group A. Regular excretors** | | | | |
| *Salm. typhi* (females) | | | | | | |
| 1 | E.B. | ----------- | ---------ox-- | xoxxoxxxxxxx | xxxoxxxoxxxx | -x- |
| 2 | F.C. | o-o-o-x-xxo- | --x-xx-xxxxx | xxxxoxxxxx-x | xxxoxxxxox-o | xx- |
| 3 | E.M. | ---xx-x-oxxx | --xxxxo-xxxx | xxxxox-xoxxx | xoxxx--xxx-- | xx- |
| *Salm. paratyphi B* (females) | | | | | | |
| 4 | F.B. | x-x---x-ooxo | --xxxxxxxxxx | x-xxxxxxxxxx | xxxxxxxx-xxx | oo- |
| 5 | M.F. | ----x-x-oxxo | -ox-xxxx-x-x | xxxxxxxxxxox | xxxxxxx--xx- | x-x |
| 6 | W.H. | x---xx--x-xx | x-xxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | xxx |
| 7 | A.K. | --x-x--xoxxx | x-xxxxxxxxxx | x-oxxxxxxxxx | xxxxxxxxxxxx | xxx |
| 8 | A.L. | --x-x-o-oxxx | ----xxx--xxx | x--x-xxxxxxx | xxxxxxxxxxxx | -xo |
| 9 | R.L. | x-x-x-x-xxxx | ---xx-oxxxxx | xxxxx-xoxxxx | xxoox-ox-xxo | xxx |
| 10 | A.P. | --------xx-x | --xx--xx-x-o | x--ox-x-xxxx | xxxxo-xxxxo- | --x |
| | | **Group B. Intermittent excretors** | | | | |
| *Salm. typhi* (females) | | | | | | |
| 11 | E.C. | --o-o-o-ooox | --o-o-oooo-o | o-o-ooooooox | xoooooooooo | ooo |
| 12 | E.H. | ---------- | x-x------ooo | ooo-oooooooo | oooooooooooo | ooo |
| 13 | E.S. | --o-----o--- | --ooooooxooo | o-oxoxxooooo | xoo-oooooooo | ooo |
| 14 | R.W. | --o-o-o-oooo | ---oo-oooooo | o-oxooooooxo | o-ooxooooooo | oo- |
| *Salm. typhi* (males) | | | | | | |
| 15 | J.F. | -xoo-oooo-oo | ooooo-o-ooo- | -ooooo-oooo | oooo--o----- | --o |
| 16 | F.M. | ox-o--xxx--- | -x-xx----xxo | xxox-xo-xo-x | --o--oo-o--- | o-- |
| 17 | H.R. | ---------- | ---------- | -ooxxox-oxoo | xoo--xo-ox-x | o-- |
| *Salm. paratyphi B* (females) | | | | | | |
| 18 | A.E. | ----x-o-xxox | --oooooooxxxo | ooxoxxxoxooo | xxxxxooxxxoo | x-- |
| 19 | N.B. | ---------- | ---------- | ---------- | -x--x--xoooo | o-- |
| 20 | E.B. | --o--xo-xooo | --o-ooooooooo | o-ooo-o-ooo- | -x--x--xooooo | oo- |
| 21 | E.C. | x---o-o---ox | --ooo-oooooo | o-xooxooooo- | ooxxoxxxooxo | oo- |
| 22 | T.D. | --o-o-x-ooox | o-oooxoox-xo | o-xoxoooooo | xoooxxooooo- | oo- |
| 23 | M.G. | ----oox-oooo | --o----ooooo | o-ooooooooo | --oooox-ooooo | --- |
| 24 | F.H. | ----oox-ooox | --ooo-oox-oo | x-xooxoxxxo- | oxoooxooxxoo | oox |
| 25 | M.I. | ----ooo-xoxo | x--xxooooooo | x-ooooooooo | ooooxooooxoo | ooo |
| 26 | S.S. | --x-o-o-oooo | --ooxxoo--xo | o-xoxxooxooo | oooxoooox-o-o | ooo |
| 27 | J.W. | oxo-o-o-ooxo | x-ooo-ooxxo- | o-oooxooxoox | oxo-xooo---x | xoo |

x, Positive isolation; o, negative isolation; -, no specimen received.

showing positive stool cultures, and by the time of submission of the first monthly specimen (July 1959) both typhoid and paratyphoid B organisms were being regularly isolated from patients in this group.

Table 3. *Excretion of typhoid or paratyphoid bacilli during and after oral Humatin therapy*

| | | Result of faecal examinations | | | |
|---|---|---|---|---|---|
| | | Daily specimens | | Weekly | Monthly |
| No. | Case | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 | | 1 2 3 4 5 6 | 1 2 3 4 5 |
| | | Humatin | | | |
| | | Group A. Regular excretors | | | |
| *Salm. typhi* (females) | | | | | |
| 1 | E.B. | o o o o o o | o x o o o o o o | o o x x x o | x x o o x* |
| 2 | F.C. | x o o o o o | x x o x o o o x | o o o o o x | o – – x x* |
| 3 | E.M. | o o o o o o | o x x o o o o x | o x x x x x | x – x – x* |
| *Salm. paratyphi B* (females) | | | | | |
| 4 | F.B. | o o o o o o | x x x x x o x x | x x x x x x | o o x x x* |
| 5 | M.F. | x o o o o o | x o x o x o x o | o o x o o o | o o o – o |
| 6 | W.H. | o o o o o o | x x x x o o x x | x x o x x x | x x x – x* |
| 7 | A.K. | o o o o o o | x x x o x o o o | x x o x x x | x – x – x* |
| 8 | A.L. | o o o o o o | x x x x x x o x | x x o x x x | x – x – x* |
| 9 | R.L. | x o o o o o | o o x x x o x x | x x x x x x | x – x – x* |
| 10 | A.P. | x o o o o o | o x x o o o o o | – – x x o o | o – x – x* |
| | | Group B. Intermittent excretors | | | |
| *Salm. typhi* (females) | | | | | |
| 11 | E.C. | o o o o o o | o o o o o o o o | o o o o o o | o – o – o* |
| 12 | E.H. | o o o o o o | o o o o o o o o | o o o o o o | – – o – x |
| 13 | E.S. | o o o o o o | o (Died 24 May 1959) | | |
| 14 | R.W. | o o o o o o | o o o o o o o o | o o o o o o | – Died August 59 |
| *Salm. typhi* (males) | | | | | |
| 15 | J.F. | o o o o o o | o o o o o o o o | o o o o o o | – – – – –† |
| 16 | F.M. | o o o o o o | o o o o o o o x | o x x o o o | x – – – o* |
| 17 | H.R. | o o o o o o | o o o o o o o x | o o o o o o | o – – – o* |
| | | (Nos. 16 and 17 positive in March 1960) | | | |
| *Salm. paratyphi* (females) | | | | | |
| 18 | A.E. | o o o o o o | o x o o o o o o | o o x o o o | o – o – x |
| 19 | N.B. | o o o o o o | o x x o o o o o | o o o o o o | o – o – o* |
| 20 | E.B. | o o o o o o | o o o o o o o o | o o o o o o | x – o – o* |
| 21 | E.C. | o o o o o o | o x x o o o o o | o o o o o o | x – o – o* |
| 22 | T.D. | x o o o o o | x o o o o o o o | o o x x o o | – – x – o* |
| 23 | M.G. | o o o o o o | o o o o o o o o | o o o o o o | x – – – o |
| 24 | F.H. | x o o o o o | o o x x o o o o | o x o o o o | o – o – o* |
| 25 | M.I. | x o o o o o | o o o o o o o o | o o o x o x | o – o – o |
| 26 | S.S. | o o o o o o | o o x x x o x o | o o o x o x | x – o – o* |
| 27 | J.W. | o o o o o o | o o o o o o o o | o o o o o o | o – o – o* |

x, Positive isolation; o, negative isolation; –, no specimen received.
* Later Examination positive for typhoid or paratyphoid bacilli (i.e. in 1960).
† Inconclusive case.

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It is more difficult to draw firm conclusions from group B for here excretion is of a more intermittent nature, but generally speaking Table 3 shows that once oral administration of Humatin ceased the majority of patients appeared to have reverted to their original excretory pattern. No enteric organisms were isolated in the immediate post-trial period from typhoid carriers nos. 11, 12, 14 and 15, or paratyphoid B carriers nos. 20, 23 and 27, but in all of these cases Table 2 shows that intervals of from 3 months to a year might elapse between successive positive isolations in which case an attempt to draw any conclusions from them regarding their carrier state after Humatin therapy can at this stage be only misleading and dangerous.

In spite of the failure of Humatin to bring about a termination of the carrier state in any one of the twenty-seven patients investigated, it was decided to complete the full programme of additional laboratory tests, as originally planned, in order to see if the results disclosed any points of interest, although significant changes were not expected. The results confirmed these expectations: there was no evidence that the exhibition of Humatin had in any way interferred with the phage-typing of the organisms isolated from the carriers and no significant changes were observed in any of the agglutinin, including Vi, titres. The haematological pictures and the results of the urine analyses were essentially the same as those obtained before treatment. Courtney, Thompson, Hodgkinson & Fitzsimmons (1960) reported that high oral dosage of Humatin may be associated with the passage of loose stools and this sign was noted in a few of the cases under test, but the administration of the drug did not result in the development of toxic manifestations which could be recognized clinically or by the laboratory tests employed. The results of a comparison of Humatin-sensitivity of the various strains of typhoid and paratyphoid bacilli before and after the trials were rather irregular, but there was some suggestion of increased resistance to the drug developing in a few cases. It is not considered that the detailed reproduction of all the laboratory findings, in the present circumstances, would provide information of greater value than this brief summary of the various investigations which were additional to the main study.

Two deaths occurred among the patients under test during the follow up period, but neither were attributable to Humatin therapy. One occurred some 5 months after receiving the drug, due to hyperstatic bronchopneumonia, but full investigation of this case was not feasible. The second case (Table 3, no. 13) was a patient who had been first admitted to this hospital in March 1952 when she was found to be suffering from schizophrenia. In 1933 she was classified as a dysentery carrier and had periodic attacks of loose stools with a raised temperature until 1936. She was first identified as a typhoid carrier in 1940 and during that year had clinically identifiable attacks of obstructive jaundice. Further attacks of jaundice with symptoms suggestive of gall-bladder disease occurred during 1940–50. The last positive isolation of *Salm. typhi* from her stool was made in May 1958, and since then her monthly routine faecal examinations have failed to reveal any enteric organisms. Death occurred on 24 May 1959 and the post-mortem was done the following day. The body was that of a slightly built adult

female without any external evidence of disease or injury. Examination of the central nervous system showed no evidence of primary organic disease on naked eye examination. The lungs were oedematous and showed bronchopneumonic changes. The heart was normal in size, but the myocardium was soft and presented a degenerate appearance. No evidence suggestive of previous typhoid infection was found at any point in the alimentary tract, or in the mesenteric glands. The most interesting gross finding was seen in the gall-bladder and biliary tract system, the former being dilated, and filled with a yellowish bile, no stones were present, and the wall was normal in thickness, being devoid of any evidence of chronic inflammatory change. The cystic duct was free from obstruction. The common and hepatic ducts were markedly dilated, and showed hypertrophic changes of the walls, suggesting a long-standing obstruction to the outflow of bile. The sphincter was intact, and dissection of the biliary system failed to show any evidence of stone, stricture, or other cause of obstruction.

Histological examination of blocks of tissue taken from all the major organs confirmed the gross findings. Section of the gall-bladder wall and cystic duct failed to show microscopical evidence of chronic inflammatory changes. Sections from the common duct confirmed the presence of hypertrophy of the muscle layers.

Using full sterile precautions samples were taken of the contents of the pyloric region, the three parts of the duodenum, the jejunum, ileum, and caecal region; colon and upper rectum, appendix, gall-bladder, cystic, common, and intrahepatic ducts, liver, spleen, sternal marrow, and urine; all being subject to bacteriological examination for enteric organisms, with uniformly negative results in each case. Death was considered to be the result of bronchopneumonia accelerated by confinement to bed as a result of the general medical condition.

## DISCUSSION

The results obtained leave little room for doubt that Humatin administered orally fails to result in a cure of the chronic enteric carrier state when this is of many years standing and biliary in type. Experimental work indicates that the drug is poorly absorbed from the alimentary tract into the blood stream and that consequently serum levels produced when the drug is administered orally tend to be low and transient. In the present series the majority of cases were most probably biliary or hepatic carriers of the chronic type, and if any chemotherapeutic agent is to be effective it must reach the bilary tract in adequate concentration either as a result of excretion from the liver into the bile, or else by the blood stream. In this connexion it would appear that when a parental preparation of Humatin becomes available it might well offer a greater possibility of success.

The fact that no enteric organisms could be isolated from the faecal specimens whilst the patients were receiving oral Humatin, supports the view that the drug if effective against enteric organisms in the gut, and though this may be due to a bactericidal effect the sudden reappearance in many of the patients in group A of the specific organism on the day following cessation of therapy suggests the

possibility that Humatin may in actual fact be exerting a bacteriostatic effect rather than a bactericidal, of sufficient magnitude to prevent the organism growing in the isolation media.

Most writers are agreed that when the enteric carrier state has persisted for more than 3 months after cessation of the primary illness the chances of spontaneous cure taking place are slight. Browning and his fellow workers (1933), however, cite several instances in the early literature in which such a cure has been stated to have occurred. Littman, Vaichulis, Ivy, Kaplan & Baer (1948) reported that in nineteen (24%) of their series of seventy-five cases, bacteriological examination of urine and faeces had remained negative for an average period of 49 months in the absence of therapy, the range being from 33 to 66 months. They believed that these cases could be referred to as spontaneously cured cases, and expressed the view that in patients cured spontaneously of the disease the gall-bladder condition had undergone spontaneous improvement, or, alternatively, that chronic inflammation and fibrosis of the gall-bladder had progressed to such an extent as to result in a functional cholecystectomy. In none of their series, however, did the opportunity arise for putting these hypotheses to the test by carrying out a post-mortem examination. Vogelsang & Bøe (1948) record the case of a woman of 35, a biliary carrier, in whom cholecystectomy revealed a chronically inflammed gall-bladder containing numerous small facetted stones. This patient continued to discharge *Salm. typhi* in the stools for more than a year after operation. An attack of jaundice of the obstructive type associated with colicky pain in the right hypochondrium followed some 2 years after operation and stool tests, together with bile culture, remained from this time negative for typhoid organisms. These authors observed that it was reasonable to assume the presence of one or more calculi in the bile ducts from which they had passed into the duodenum during her attack of biliary colic, resulting in the cessation of the carrier state.

The clinical picture in the case of patient no. 13 of the present series bears a strong resemblance to that reported by Vogelsang & Bøe (1948). In this case also periodic attacks of obstructive jaundice and biliary colic suggested impaction of a stone in the bile duct system, and it is the writer's view that this patient also underwent spontaneous cure as the result of the pasage of an obstructing calculus from the common duct during one of her attacks of biliary colic, the general dilation of the duct system and hypertrophy of the wall of the common duct met with at post-mortem suggested that an obstruction of some standing had been present at one time or another. Post-mortem examination failed to reveal the nature of the obstruction, and bacteriological examination showed that the patient was not a carrier at the time autopsy was carried out. The experience in this case of spontaneous cure of the chronic typhoid carrier state, together with that of Vogelsang & Bøe's (1948) case adds support to the statement by Browning and his colleagues (1933) that in these rare cases of spontaneous cure, the persistance of the carrier state is the result of some such mechanical cause as the presence of a calculus within the bile duct system.

## CONCLUSIONS

From the results of bacteriological examination for enteric organisms of the stool specimens from patients in category A it is justifiable to conclude that in the chronic biliary typhoid and paratyphoid B carrier of long standing oral Humatin, whilst apparently rendering the faeces free from the specific organisms during the period of administration of the drug, fails in the dosage given to affect the excretion of these organisms beyond this period, thus failing to produce a cure of the carrier state.

Although not conclusive, the results of *in vitro* sensitivity tests of *Salm. typhi* and *Salm. paratyphi B* to Humatin partial sulphate (75%) suggest that strains resistent to the action of the drug might have developed.

## SUMMARY

A clinical trial to determine the effect of oral Humatin therapy on the course of the chronic enteric carrier state in a group of twenty-seven typhoid and paratyphoid B carriers is described. It is concluded that the drug when administered orally in this group of carriers fails in the dosage given to effect a cure of the carrier state.

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