

cases were found to have lymphocytic infiltrates in the hepatic sinusoids on liver biopsy and a significantly raised antibody titre for malaria, and 26 of the 29 had palpable splenomegaly. This syndrome is called locally big spleen disease. These 29 cases constitute a special group, and are described in detail.

Thirteen patients presented with acute haemolytic episodes shown by acholuric jaundice and high reticulocyte counts. Such acute episodes have not been seen in 90 non-pregnant cases with this syndrome.

Non-pregnant cases have all been shown to have a shortened red-cell survival of varying degrees. It is concluded that the pregnant patients have a chronic low-grade haemolytic process which predisposes them to acute haemolytic episodes during pregnancy. The possible factors producing these acute attacks and the danger to the mother and foetus are discussed.

Big spleen disease is believed to be an abnormal immune response to malaria. It should be suspected when splenomegaly is found, and can be diagnosed by liver biopsy. Pregnant women with this condition with or without anaemia should be treated with a course of 15 mg. of primaquine daily for 15 days coupled with a curative course of chloroquine and followed by prolonged chemoprophylaxis against malaria throughout pregnancy and in all subsequent pregnancies.

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Chronic Enteric Carriers: Management of Personal Problems*

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The enteric fevers (typhoid and paratyphoid A, B, and C) have been known to man for many centuries, although it is comparatively recently only that their incidence has decreased in lands with high standards of sanitation. In Western Europe, however, epidemics still occur, usually when the basic principles of hygiene have been lowered in association with direct or indirect contamination of food or water-supplies by a carrier. During the past 30 years such notable epidemics of typhoid have occurred in Bournemouth in 1936, Croydon in 1937, Zermatt in 1963, and Aberdeen in 1964. In 1963 there were simultaneous outbreaks of paratyphoid B in East Anglia, Surrey, Yorkshire, and the Edinburgh area, with frozen Chinese egg as the common source of infection (*Brit. med. J.*, 1963). Paratyphoid A and C seldom occur primarily in the United Kingdom, being almost invariably imported from other lands.

According to Leff (1957), about 10% of all convalescent typhoid patients excrete typhoid bacilli for three months after infection, with 2 to 5% becoming chronic carriers. In Edinburgh in 1963 11 (5.8%) out of 188 persons infected were still excreting *Salmonella paratyphi B* after three months (Sharp *et al.*, 1964), of whom six (3.2%) became chronic carriers. Of the two types of enteric carrier the faecal excreter is more common than the urinary excreter. The chronic carrier state may be predisposed to by pre-existing gall-bladder or renal infection, but may also follow acute cholecystitis or pyelitis as a complication of enteric fever. In some instances, also, a person may become a chronic carrier without any relevant past history. Surgical removal of the gall-bladder or kidney is not

always successful in curing the chronic carrier state. Numerous claims have also been made periodically about the efficacy of various antibiotics, of which only long-term ampicillin has given encouraging results to date (Christie, 1964). When a permanent medical or surgical cure becomes available the carrier problem may not necessarily be completely resolved. Many carriers, disappointed by previous failures and in good general health, may be unwilling to undergo further treatment, even if this does not involve surgery and its attendant risks. Medical problems may present in toxic reactions to antibiotics, while social problems may be associated with prolonged absence from the home or work. There may be additional surgical problems with carriers who have multiple foci of infection of the biliary or urinary tracts, requiring excessively radical measures.

Carriers employed as food-handlers can be legally excluded from this occupation (*Statutory Instrument*, 1959). These measures are necessary to safeguard the public health, but such carriers are faced with the problem of finding other employment and learning new trades, often in middle or later life. However, as many carriers are women, food-handling does not end there, but continues in the home, where families may have to be fed. Difficulties may arise with individuals in achieving a balance between periodical supervision and the emphasizing of personal hygiene, with the potential danger of creating "leper neuroses." Involvement of the central nervous system, and varying degrees of mental confusion and apathy, are not uncommon clinical features of enteric fever, which in some cases may have residual effects in post-enteric psychoses and allied states. These have been known to persist for some months, although views differ on whether mental recovery is thereafter complete or not. Such persons who continue to excrete the organism may readily become permanently neurotic.

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Present Investigation

In an attempt to understand more fully the personal, social, and environmental problems of chronic enteric carriers the 18 known excretors in the City of Edinburgh were interviewed individually. A standard questionnaire was used, which inquired particularly into any changes in their way of life, in dietary habits, and in social or occupational status; also regarding their attitudes towards the infection, the failure of treatment, and being supervised by the public health department. As there had been some recent amendments in the management of carriers in the city, it was also thought worth while to compare two groups of carriers, each consisting of nine persons, who were discovered before (group I) and after (group II) the paratyphoid outbreak of 1963.

Before 1963, enteric cases on discharge from hospital were followed up bacteriologically for a few weeks only. Those whose excretion continued were followed up for a longer but variable period, and on failure to achieve clearance their names were added to the carrier register. Further follow-up was largely dependent on sanitary inspectors, and contact with many of the earlier carriers became very tenuous. Since early 1963, following agreement among physicians, bacteriologists, general practitioners, and the medical officer of health, all enteric cases on discharge from hospital are subjected to an intensive bacteriological follow-up for a minimum of six months. This follow-up is arranged by a medical officer from the public health department, who advises, where necessary, on the many varied problems which may arise. In the early months of continued excretion further courses of antibiotic treatment may be given if advised by the physicians. Thereafter investigation of the biliary or urinary tract is carried out, surgery being performed only if indicated on clinical grounds. Further bacteriological follow-up is again supervised by a medical officer, but is considerably relaxed after 12 months of excretion. By this time the relationship between the health department and the carrier has become well established. Thereafter contact is maintained at intervals varying between six months and one year.

The criterion of a chronic enteric carrier for the purpose of this study is the bacteriological isolation of the organism 12 months or longer after infection or notification. The known carriers in Edinburgh consist of one typhoid urinary excretor, and one paratyphoid A and 16 paratyphoid B faecal excretors. One of the paratyphoid B excretors is resident outside the city but was employed and infected in Edinburgh during 1963; for this reason, and with the consent of the neighbouring health department, Edinburgh has maintained contact with her on several occasions since. All the carriers are female, with the exception of the typhoid and paratyphoid A excretors, and one of the paratyphoid B excretors. The age range extends from 19 to 83 years (Table I); the time range of known carriage varies from 15 months to 31 years.

TABLE I.—Age/Sex Distribution of the Carriers

| Age Group: | 0-14 | 15-24 | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75+ | Total |
|------------|------|-------|-------|-------|-------|-------|-------|-----|-------|
| Male | — | — | — | — | — | 2 | 1 | — | 3 |
| Female | — | 1 | 2 | — | 3 | 4 | 1 | 4 | 15 |
| Total | — | 1 | 2 | — | 3 | 6 | 2 | 4 | 18 |

For the purposes of further identification brief details are given of the social, epidemiological, and clinical histories and the personality types of the individual carriers in the two groups under study (labelled A to J and R to Z).

TABLE II.—Number of Individual and Total Courses of Antibiotic Treatment in the Two Carrier Groups

| Group I Carriers | | | | | | | | | | Group II Carriers | | | | | | | | | |
|------------------|---|---|---|---|---|---|---|---|-------|-------------------|---|---|---|---|---|---|---|---|-------|
| A | B | C | D | E | F | G | H | J | Total | R | S | T | U | V | W | X | Y | Z | Total |
| 1 | 1 | 3 | 2 | 3 | — | 2 | 1 | 2 | 15 | — | 4 | 6 | 2 | 4 | 1 | 2 | 4 | 4 | 27 |

Group I (A-J) : Carriers Discovered Prior to Paratyphoid Outbreak of 1963

Faecal Carrier of *Salm. paratyphi* A

A; married man, aged 65; intelligent and sensible; employed as a draughtsman; intermittent excretor for at least eight years. Phage-type 1. Discovered after diarrhoeal upset; previously had "gastro-enteritis" in Burma in 1932. Antibiotic treatment only.

Faecal Carriers of *Salm. paratyphi* B

B; widow aged 71; cheerful, extroverted personality; lives alone; continuous excretor for at least seven years. Type 1. No history of enteric illness; discovered on contact investigation following infection of granddaughter. Antibiotic treatment and gall-bladder investigation.

C; widow aged 59; very introspective and emotionally unstable; lives alone; continuous excretor for 25 years. Type 1. Discovered on contact investigation of neighbour's child, with whom she shared toilet facilities. Two other cases 10 years later. Antibiotic treatment and gall-bladder investigation.

D; married woman aged 52; excitable but sensible; housewife; intermittent excretor for seven years. Type 2. Discovered on contact investigation after infection of daughter and granddaughter. Antibiotic treatment and gall-bladder investigation.

E; married woman aged 54; fairly intelligent and placid; housewife and part-time insurance agent; continuous excretor for at least five years. Type Taunton. No history of enteric illness; discovered on contact investigation after infection of daughter and a child visitor. Antibiotic treatment and cholecystectomy, although no gall-bladder symptoms or pathology.

F; widow aged 80; intelligent, slightly introspective; lady's companion until three years ago; continuous excretor for 19 years. Type 3a. Discovered after diarrhoeal illness. Two grandchildren infected two years later. No antibiotic treatment.

G; widow aged 81; excitable and introspective; lives alone; intermittent excretor for five years. Type Taunton. Infected during small outbreak in 1961; granddaughter also infected. Antibiotic treatment only.

H; widow aged 83; placid, dull personality; lives alone; continuous excretor for at least seven years, but recalls that sister had "typhoid" in 1894. Type 1. Discovered after "gastro-enteritis." Antibiotic treatment only.

J; bachelor aged 63; fairly intelligent, but introspective; retired printer's assistant; lives alone; continuous excretor for 29 years. Type 3a. Mother (who died from paratyphoid fever) and sister subsequently infected. Antibiotic treatment only.

Group II (R-Z) : Carriers Discovered Since Paratyphoid Outbreak of 1963

Urinary Carrier of *Salm. typhi*

R; married man aged 62; fairly intelligent and placid; employed as a hotel linen-porter; intermittent excretor for 31 years. Phage-type Fl. Not discovered as carrier until contact investigation after wife's infection in 1965. No antibiotic therapy; surgery also contraindicated by multiple foci of infection of urinary tract.

Faecal Carriers of *Salm. paratyphi* B

S; spinster aged 31; very intelligent and cheerful personality; clerk; continuous excretor for three years. Type Taunton. Infected during outbreak of 1963, when she had an acute clinical relapse. Antibiotic treatment and cholecystectomy following acute cholecystitis nine months after infection—no previous gall-bladder symptoms.

T; spinster aged 19; apparently cheerful, but introspective; clerk; continuous excretor for three years. Type Taunton. Infected during outbreak of 1963; sister also infected. Antibiotic treatment and gall-bladder investigation.

U; widow aged 64; placid, dull personality; housewife; continuous excretor for three years. Type Taunton. Infected during

outbreak of 1963; daughter and granddaughter also infected. Antibiotic treatment only; unwilling to be readmitted to hospital for further investigation.

V; married woman aged 80; pleasant and sensible; housewife; continuous excreter for three years. Type Taunton. Infected during outbreak of 1963; husband, two daughters, and granddaughter also infected. Antibiotic treatment; unwilling to be readmitted to hospital for further investigation.

W; married woman aged 53; placid, dull personality; housewife; continuous excreter for at least 18 months. Type 1 var. 8. No history of enteric illness; discovered at cholecystectomy for chronic gall-bladder dyspepsia. Antibiotic treatment also given.

X; spinster aged 27; very intelligent, but introspective; university research worker; intermittent excreter for 15 months. Type Stirling. Discovered following "gastro-enteritis"; flat-mate also infected. Antibiotic treatment and gall-bladder investigation.

Y; spinster aged 62; excitable and introspective; "retired" shop assistant; lives alone; continuous excreter for three years. Type Taunton. Infected during outbreak of 1963; discovered during investigation of bakery employees. Antibiotic treatment and cholecystectomy; calculi and previous history of gall-bladder dyspepsia.

Z; married woman aged 45; introspective, but sensible; housewife and part-time clerk; continuous excreter for three years. Type Taunton. Infected during outbreak of 1963; son also infected. Antibiotic treatment and cholecystectomy—previous history of cholecystitis.

Clinical Aspects

Fifteen of the carriers had a clinical history of enteric fever or "gastro-enteritis." Only three carriers (B, E, and W) gave no history of enteric fever or other gastro-intestinal or febrile upsets.

Eight persons in all had a history of symptoms relating to the gall-bladder or urinary tract; four of them were treated surgically. One other person (E), despite the absence of symptoms or radiological abnormality, has also had her gall-bladder removed in an unsuccessful attempt to cure her carrier state. Of the 13 carriers who were not treated surgically three had complained of occasional gall-bladder dyspepsia, only one of whom (V) declined further investigations.

All except two have had at least one course of antibiotic treatment (Table II). F was diagnosed in 1946 prior to the use of chloramphenicol in the treatment of enteric fever (Woodward *et al.*, 1948), since when, despite her grandchildren's subsequent infection and her employment as a lady's companion, she had never been readmitted to hospital for further investigation or antibiotic treatment. Antibiotics and surgery were contraindicated for R because of the multiple foci of infection of his urinary tract and the extreme intermittency of his excretion. Five of the six carriers infected in 1963, three of whom have also had surgical treatment, have had four or more courses of antibiotic treatment with chloramphenicol, ampicillin, neomycin, and/or cephaloridine (*Brit. med. J.*, 1964). These antibiotics were given for periods varying from 10 days (neomycin) to six weeks (ampicillin).

Five persons expressed continued interest in returning to hospital for further investigation and treatment, of whom three only (B, J, and Y), with no occupational or family commitments, were prepared to be readmitted unconditionally.

Occupational Aspects

Three women left their employment as a result of infection, while a fourth (T) had been unable to proceed with her intended career as a children's nurse. At a later date she was also turned down by the Australian immigration authorities because of her carrier state. Y was discharged from her occupation as a bakery shop-assistant. Although she was paid some compensation by her employers, in whose premises she had been infected, if she had been resident in England and Wales she would have been eligible for further compensation by the local health authority under Section 41 of the Public Health Act, 1961. There are, however, no legal provisions in Scotland as yet for financial aid to workers excluded from employment in the interests of the public health. She declined to seek other employment because of her age, as also did U, who had been employed as a cleaner. As a result of continued ill-health, which included further attacks of cholecystitis and subsequent surgery, Z resigned from her post as a school secretary, but has since been employed within the public health department.

In contrast was the case of S, whose employers, despite her absence for over a year, would not accept her return to work until they had installed toilet facilities for her exclusive use.

Personal and Social Aspects

Specific inquiries were made regarding personal and social aspects of the carrier state. The distribution of the related psychological disturbances of the individual carriers in the two groups was compared. The results are summarized in Table III.

Emotional upsets or nervous breakdowns of varying severity and duration were admitted by six persons, four of whom had consulted their family doctor for advice or treatment. Of these C has been the most seriously affected. She has a decided "leper complex," regarding herself as a social outcast and believing that people watch her to ensure that she does not handle food. During the summer of 1964 Y felt that she had been losing control of herself and had wanted to "run away." After her gall-bladder operation Z also suffered from acute emotional instability and squeamishness, which she attributed to a fear of her liver being infected. After her infection in 1959 D had had a severe nervous breakdown, arising principally from the accidental death of her son-in-law, which occurred while she, her daughter, and her granddaughter were in hospital. As the index case, she largely blamed herself for having precipitated the unhappy chain of events. Her emotional instability at that time may also have been accentuated by the menopause. The two youngest carriers (T and X) also suffered from emotional instability, particularly during the early months. Despite having been the more distressed initially, and having the added disappointment of bacteriological relapse after six months apparently free from infection, X has since been able to accept her carrier state more readily than T. The latter, however, had perhaps suffered more in respect of her proposed future career.

Ten carriers, all female, had experienced disappointment or depression following antibiotic or surgical failure. In some instances, particularly in the group II carriers who had been

TABLE III.—Distribution of Adverse Psychological Responses to Personal and Social Aspects of the Carrier State

| Personal and Social Aspects | Group I Carriers Discovered Before 1963 | | | | | | | | | | Group II Carriers Discovered Since 1963 | | | | | | | | | |
|--|--|---|---|---|---|---|---|---|---|-------|--|---|---|---|---|---|---|---|---|-------|
| | A | B | C | D | E | F | G | H | J | Total | R | S | T | U | V | W | X | Y | Z | Total |
| General emotional instability .. | — | — | 1 | 1 | — | — | — | — | — | 2 | — | — | 1 | — | — | — | 1 | 1 | 1 | 4 |
| Depressed by failure of treatment .. | — | — | 1 | 1 | — | * | — | — | — | 4 | — | — | 1 | — | — | — | 1 | 1 | 1 | 6 |
| Self-imposed social restrictions .. | — | — | 1 | 1 | — | — | — | — | — | 5 | — | — | 1 | — | — | — | 1 | 1 | 1 | 5 |
| Fear of child-care responsibilities .. | — | — | 1 | — | — | — | — | — | — | 2 | — | — | 1 | — | — | — | — | 1 | 1 | 4 |
| Disturbed by supervision .. | 1 | — | 1 | — | — | 1 | 1 | — | — | 4 | — | — | — | 1 | — | 1 | — | — | 1 | 4 |
| Totals | 1 | 2 | 5 | 3 | 1 | 1 | 3 | — | 1 | 17 | — | 1 | 4 | 1 | 3 | 1 | 4 | 4 | 5 | 23 |

* No antibiotic or surgical treatment.

given almost twice as many antibiotics as group I (Table II), this was accentuated by repeated failures. Moods of depression still occasionally trouble T. A loss of faith in the medical profession was admitted by Z, although this has been modified since joining the public health staff. Six were unaffected by the failure of treatment, of whom B, H, U, and W were all of relatively low intelligence and tended to be apathetic about their infection. Two carriers (F and R) had neither antibiotic nor surgical treatment.

Self-imposed social restrictions, such as being reluctant to entertain or to attend clubs or meetings, were applied by 10 carriers, although D and X had relaxed these after the first six months. The youngest carrier (T), however, has almost completely given up going out with her friends, while J has never left Edinburgh on holiday, other than for day excursions. In only two instances had relationships with family or friends been seriously affected. Although often invited, the friends of G no longer visit her house, and her relatives make excuses about having meals, which has reinforced her fear of entertaining. Although unable to specify the change in relationship with her friends, Y attributed this to her not inviting them to her home. In addition, C has never disclosed her carrier state to her married daughter, but has always been able to arrange for meals to be prepared by others. An interesting result of the 1963 outbreak was the formation of a small social group among S, T, Y, and Z. All four women had been in hospital together, and, although of differing social backgrounds, have since maintained their relationship, exchanging Christmas cards and meeting periodically in each other's homes.

When asked their attitude to supervising children, six carriers were particularly concerned about transmission of infection, of whom four (B, C, V, and Z) had already caused secondary infection. Since their own infection T and Y have never undertaken the care of young children. Of the 12 who had no such fears six had previously been responsible for having infected seven children, mainly grandchildren.

Eight persons, four in each group, admitted being upset to a greater or less extent by supervision. Visits to C always resulted in her becoming very emotionally distressed, and further supervision was referred to the family doctor. G was also considerably upset, particularly when a long time interval had elapsed since she was previously visited. Some personal disturbance was admitted by A, although he maintained that he should not be forgotten. Although F denied ever being upset, she nevertheless had declined initially to be interviewed during the present study. Of the four group II carriers the placid nature of W and the common-sense approach of X helped in overcoming their initial distress. Even before joining the health department Z was always apparently anxious to cooperate, but until recently had never admitted her previous resentment. Although she welcomes regular contact, U has always feared enforced return to hospital following positive bacteriology reports, and has often been most reluctant to submit samples. Of the others seven had no specific observations about supervision, having accepted its necessity, while the remaining three (E, V, and Y) also preferred regular contact.

Attitudes to domestic cooking duties, acquired dietary fastidiousness, separate laundering of personal articles from those of other household members, and literary habits were factors not equally applicable to all carriers, and were therefore excluded from Table III.

Only A and R, who are married men, have no domestic cooking duties. Ten carriers prepare meals for families, although T avoids these duties as often as possible. All are fully aware of their responsibility regarding personal hygiene, but only C has apparently become obsessed by this. Six carriers live alone and prepare their own meals. Not unexpectedly, six of the seven whose source of infection had been traced to bakery confectionery goods during the para-

typhoid outbreaks of 1961 and 1963 had never since patronized or consumed goods from the bakery incriminated in both instances. Only V, whose husband is a former employee of the bakery, has not made any change.

Separate laundering of personal articles of clothing was considered an essential precaution by U, X, and Z, although they had never been so instructed. Seven persons admitted an interest in medical literature since their infection, four of whom (J, S, X, and Z) had acquired a very good understanding of the epidemiology of enteric fever. Genuine interest only was shown by S and X in particular, who did not consider that they had studied excessively. Only J, living alone, might have taken an abnormally excessive interest.

Only two persons (H and R) had apparently not been affected in any manner. This was perhaps not unexpected, with their basically placid personalities, reinforced by the apathy of H and the philosophical attitude of R.

Discussion

It would appear that a good liaison with carriers has no effect in minimizing the occurrence of psychological disturbances associated with the carrier state (Table III). Although the number of excretors investigated is inadequate for any statistical significance, this relationship may even contribute towards emotional distress in some cases by the emphasis placed on the importance of personal hygiene and also the regular contact with the health department. There is no case for the argument, however, that without supervision carrier neuroses would not occur. In the United Kingdom such control measures are necessary to minimize the risk of spread of endogenous infection within the community. Nevertheless, considerable care must be taken to avoid subjecting carriers excessively to a series of unsuccessful antibiotics, in addition to bacteriological, radiological, and surgical procedures, as these may only raise false hopes of cure.

Any group of individuals taken at random, such as the 2 to 5% of enteric patients who become chronic carriers, will contain a range of varying personality types. Five of the eight persons who had taken some exception to supervision were introspective about their infection; of these C, F, and G in group I became increasingly divorced from the health department, while liaison with X and Z in group II steadily improved. It is believed that T, X, Y, and Z might readily have become as permanently neurotic about their carrier state as C in group I. Although having a few residual problems, all of them agree that regular contact with medical officers and the mutual interchange of visits and experiences of T, Y, and Z in the company of S, who had been able to adapt herself much more easily, have helped considerably. Might there also be a place for organized group therapy?

Although C is undoubtedly the most seriously affected carrier, T perhaps may present the greater future problem. She was at a very impressionable age, having only recently left school when she became infected three years ago, since when her life has already been considerably disturbed. In addition, she has had more antibiotic treatment than any other carrier (Table II). Like S and X, she is a young unmarried woman. What additional problems may arise if marriage is considered, although none admit this possibility at the time of writing? What would be the average young man's attitude towards marrying one of these young women? If they do marry and become pregnant, childbirth will be conducted in an isolation ward under antibiotic cover, and fears about infant-feeding may arise. Many of the other carriers, particularly those over 65 years of age, are much less of a problem. Their way of life is much more settled, and, like V, who has died since this study started, their remaining carrier life is relatively short.

The City of Edinburgh, with its geographical compactness and population of less than half a million, is perhaps an

optimum size for a public health department to have an infectious diseases epidemiological section, whose medical staff can devote some time and effort to the management of chronic enteric carriers. There is no doubt in my mind that a close liaison with carriers is very desirable for all concerned. This should of course be primarily the responsibility of the medical officer of health rather than the individual family doctors. The relationship should begin in hospital with all enteric cases, whether they subsequently become carriers or not. The emotional support given to potential carriers in the early months after discharge from hospital can be invaluable in establishing the relationship even in the more acutely disturbed cases where the family doctor may also be involved. In a larger study of enteric carriers in Western Germany, Rasch (1964) also concluded that more attention should be given to the medical and social welfare of carriers. Every carrier in group II is readily approachable at any time. In group I there are some who are either relatively unapproachable or who still resent their having been "neglected," with sporadic visits only from a sanitary inspector, with whom they were often reluctant to discuss personal problems related to their carrier state.

Summary

The personal, social, and environmental problems of the 18 chronic enteric carriers in the City of Edinburgh are described and discussed. A comparison is made of the acquired psychological disturbances of two numerically equal groups of carriers, discovered before and after an outbreak of paratyphoid B in 1963, in relation to their public-health management.

Brief details are given of social, epidemiological, and clinical histories and personality types of the individual carriers.

Only two carriers had not been upset at all, while one at least had acquired a decided "leper complex." Some concern is felt about the younger carriers who are unmarried women and have a greater remaining life expectancy, particularly the youngest, aged 19, who was infected soon after leaving school and has already had her life considerably disturbed.

A close liaison between the public health department and individual carriers appears to have no effect in minimizing the occurrence of psychological disturbances, but there is no doubt in my mind of the desirability of such liaison for all concerned.

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Ampicillin for Persistent Typhoid Excreters, including a Clinical Trial in Convalescence

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One of the most serious consequences of typhoid fever is the carrier state. Approximately 30% of patients may still excrete *Salmonella typhi* immediately after completing treatment, but almost 90% of those become negative within one month (Vogelsang and Bøe, 1948). Anderson and Richards (1948) found that all nine convalescent excreters out of 110 cases cleared spontaneously. However, usually about 3% of patients contracting typhoid fever become chronic carriers—that is, they are found to be excreting *Salm. typhi* continuously or intermittently after a period of from six to twelve months following recovery from the acute stage of the illness.

When typhoid fever occurred in Aberdeen in 1964 (Walker, 1965) it was decided to follow the suggestion of Christie (1964) and test the efficacy of ampicillin in preventing the carrier state. With a possible total of 500 or more cases of typhoid, about 160 temporary and 16 chronic carriers might be expected. It was therefore decided to conduct a double-blind trial of ampicillin in early convalescent excreters by means of a strictly random allocation of identical ampicillin and inert capsules. It was not thought that there would be sufficient patients for testing more than one drug or one duration of treatment. In view of the wide publicity which attended this outbreak and

the treatment of the patients, it was considered necessary to explain fully to the patients the conduct of and reason for the trial and to invite them to participate. It was also agreed to carry out a sequential analysis of the results, so that if ampicillin were clearly of value the trial would be stopped and all excreters treated with it. In the event, sequential analysis gave no clear result.

Conduct of Trial

The trial was timed as early in convalescence as was feasible, since most patients were feeling well and were anxious to return home. The agreed criteria for discharge from hospital were three negative specimens of both stool and urine at four-day intervals beginning four days after the end of the initial treatment. It was therefore decided that any positive specimen occurring during this period would make the patient eligible to enter the trial provided that certain additional criteria were fulfilled. These were: (1) no known penicillin sensitivity, (2) no other antibiotic therapy at that time, and (3) the consent of the patient after having the double-blind nature of the trial, and its purpose, fully explained.

The dosage of ampicillin was 1 g. six-hourly for adults, 0.75 g. six-hourly for children aged 6-12 years, and 0.50 g.

* From the City Hospital, Aberdeen.