SUCCESSFUL TREATMENT OF A CHRONIC PARATYPHOID CARRIER WITH SULPHAGUANIDINE

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It is generally recognized that human beings are the only source of the causative organisms of the enteric fever group and that carriers play an important part in spreading these diseases. One would probably be justified in saying that most of the outbreaks of paratyphoid fever in this country during the last few years had their origin in carriers. Medical treatment of the carrier condition has been found of no avail, and nothing had arisen up to the outbreak of war to alter the conclusion reached by Browning (1933) and his colleagues that cholecystectomy or other surgical measures directed towards the gall-bladder alone hold any prospect of cure.

While sulphanilamide itself and its earlier derivatives had been found to have little therapeutic action on intestinal infections, the introduction by Marshall and his collaborators (1940) of sulphaguanidine with its high bacteriostatic activity and low absorption from the intestinal tract seemed to offer good chemotherapeutic possibilities. Very soon favourable results were reported in the treatment of bacillary dysentery, and it was the favourable impression one of us (H.L.) gained in the treatment of some minor outbreaks of Sonne dysentery that induced us to try this drug in a paratyphoid carrier in spite of the fact that sulphaguanidine had failed to cure dysentery carriers. The typhoid carrier whose cure had been reported by Levi and Willen (1941) was not a chronic carrier, and it is impossible to say whether sulphaguanidine played any part in it.

Case Record

Our patient, Mrs. F., aged 24, a wartime nurse in the E.M.S., contracted the disease while nursing a case of paratyphoid fever. The febrile period of the disease, which lasted for rather more than a month, started on Sept. 3, 1941. She made an uneventful recovery, but continued to excrete *Bact. paratyphosum* B in the stools. Cholecystectomy was performed on Jan. 2, 1942, but the result of this surgical intervention was disappointing, for the carrier state continued unabated.

In July, 1942, Mrs. F. moved into the area served by this laboratory, and after an examination of her faeces had shown profuse growth of *Bact. paratyphosum* B it was decided to try treatment with sulphaguanidine. The first course, which was begun on Aug. 3, consisted of 1.5 g. three times a day for three days, followed by 1.5 g. twice a day for two days—19.5 g. in all; the patient was ambulatory during treatment. It might be mentioned that owing to a misunderstanding the amount of sulphaguanidine received by the patient in this first course was only half that intended.

Several bacteriological examinations from Aug. 10 onwards proved entirely negative for paratyphoid bacilli until Aug. 27, when they started to reappear. At first their number was small and growth could be obtained only after enrichment in tetrathionate broth; but they gradually became more numerous, until finally *Bact. paratyphosum* B was again the prevailing organism on MacConkey and desoxycholate-citrate agar plates sown directly with the faeces.

Though the result of this first attempt fell short of our expectations the temporary disappearance of the infective organism, which had not previously been observed in this carrier, was so striking that we could only attribute it to the administration of the drug. Hoping that continued treatment might exercise a cumulative effect, the patient underwent a further course of sulphaguanidine treatment, which began on Sept. 22. On this occasion the patient, whose weight was approximately 9 st., received 50 g. in seven days. This time complete suppression of the paratyphoid bacilli did not occur, but their number was greatly reduced. A third course was started on Nov. 24, the same dose again being given.

Though all subsequent examinations proved negative for paratyphoid bacilli the patient was given a similar and final course in Jan., 1943. *Bact. paratyphosum* B was never again recovered in

six further examinations (Jan. 14, Feb. 2, 16, March 5, April 9, and May 8), and the patient has been clear now for about six months.

Discussion

Can her carrier condition be considered cured? It is a well-known fact that carriers sometimes cease to excrete the infective organisms for periods of several months, and the failure to recover *Bact. paratyphosum* B from this patient's stools for six months would not by itself justify the conclusion that she has been cured. But we have been fortunate in having the collaboration of Dr. A. Felix of the Emergency Public Health Laboratory Service, whose investigations offer strong evidence of the cure of our patient's carrier state.

According to recent unpublished work by Felix a Vi agglutination test, similar to that employed in the examination of chronic typhoid carriers (Felix, 1938), is often an aid to the detection of chronic carriers of *Bact. paratyphosum* B. A steady or rising B Vi titre is suggestive of a probable chronic carrier state, whereas a decreasing B Vi titre in a carrier would indicate that the carrier state was only temporary. With Dr. Felix's consent we reproduce his findings and conclusion:

"The following readings were obtained in the various agglutination tests:

		9/9/42	15/3/43
B. paratyphosum B Vi	..	1:40 +	1:20 ±
" O	..	1:200 ±	1:100 ±
" H sp.	..	1:200+ ±	1:100 ±
Salmonella H group	..	1:100+	1:50 +

"I think that this result indicates that Mrs. F. no longer harbours paratyphoid B bacilli—that is to say, her carrier condition has been cured."

In the summer of 1942, when we decided to give sulphaguanidine a trial in the treatment of our paratyphoid carrier, the recent American literature on the subject was not available in this country. Had we seen it, it is unlikely that we would have tried sulphaguanidine, as the result of a number of well-conducted trials in enteric carriers (Cutting and Robson, 1942; Watt and Peterson, 1942; Saphir, Baer, and Plotke, 1942) had been unconvincing. Those reported successes were restricted to a very few cases, and either the patients treated were not chronic carriers or the data published were not sufficient to allow of a decision on this important point (Hoagland, 1942). We know now also, from personal communications, that previous trials in this country were no more successful.

Before we try to find an explanation for the discrepancy between our own experience and the recent American findings we have to consider the effect of cholecystectomy on the carrier condition. It is known that the infective organisms can persist in the faeces for weeks or even months after the removal of the gall-bladder (Browning, 1933). Though there seems to be general agreement that the onset of the beneficial effect of this operation is not usually delayed beyond three months, Browning (1933) describes the case of a paratyphoid carrier who continued to excrete the specific bacilli for a period of 14 months after cholecystectomy before finally ceasing. Thus, in order to assess the part of sulphaguanidine treatment in the cure of our carrier we have to keep in mind that this occurred approximately nine months after cholecystectomy. But we think we have better evidence for the efficacy of the drug in our case.

As described above, the drug had an immediate and striking effect on the number of *Bact. paratyphosum* B excreted. It would seem unreasonable to suppose that this disappearance of the infective organism from the stools, which had never before been observed in this patient, was solely a late effect of cholecystectomy. Furthermore, after the first course of treatment the paratyphoid bacilli reappeared, to become just as numerous as before; only after two additional courses did they disappear definitely. And here our findings are in agreement with those of Cutting and Robson (1942), who also found a diminution and a temporary disappearance of *Bact. typhosum* in the faeces of a carrier after a course of sulphaguanidine.

We feel, therefore, that the success in the treatment of our chronic paratyphoid carrier was due to the cumulative effect of repeated courses of sulphaguanidine, and publish this case in the hope that others may succeed in reproducing our experience.

Our thanks are due to Dr. A. Felix for his collaboration, and to Prof. S. P. Bedson, Sector Pathologist, E.M.S., for his interest in this investigation.

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Medical Memoranda

Actinomycosis of the Tongue successfully Treated by Sulphonamides

The following case record may be considered interesting enough to merit publication.

In May, 1941, a farmer aged 59 had a fluctuating swelling in the substance of the tongue to the right of the middle line. It was aspirated and smears were sent to Dr. Eric Wordley, pathologist, Plymouth, who reported the presence of the ray fungus. The patient was given large doses of potassium iodide, but developed iodism so badly that the treatment had to be stopped after 10 days. He was then given three courses of sulphapyridine 4 g. daily for four days, with an interval of four days between each course. The swelling of the tongue was smaller after the aspiration, and it diminished still more under treatment. In Aug., 1941, it had disappeared and there was no palpable induration. In Sept., 1941, he had lobar pneumonia and again received sulphapyridine treatment for three days. His recovery was uneventful. Incidentally, he has had glycosuria for many years.

He was seen at intervals of six months, and now (May, 1943) the tongue remains normal. Except for the two upper canine teeth, which look healthy, he is edentulous and wears upper and lower dentures; it is therefore unlikely that the entry of infection was through a tooth socket. In the autumn of 1940 one of his bullocks had "wooden tongue," and there may have been direct hand-to-mouth infection from that source.

The medical department of Messrs. May and Baker kindly supplied me with copies of the more important published papers on the subject of treatment of actinomycosis by sulphonamides.

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Arteriovenous Aneurysm of Neck

The following remarkable case is thought worthy of being placed on record.

CASE RECORD

A soldier aged 25 reported sick with attacks of swelling of the neck for the past six years which recurred every few weeks and at times prevented his wearing a collar. Attacks were associated with malaise and an aching pain in the left side of the neck which radiated to the shoulders. Sometimes there was slight dyspnoea and wheeziness, and he felt faint and sweated freely. A small nodule above the left clavicle often enlarged and became tender in the attacks. Throbbing in the left side of the neck and a sense of suffocation were usually brought on by a change in the weather, especially if thunder was about.

On examination he was healthy in appearance, and of good general physique; there was a small scar just above the lower end of the right sternomastoid. Increased pulsation was visible on the left side of the neck, and a systolic thrill was palpable over an area 2 in. in diameter at the level of the thyroid cartilage. Slight expansile pulsation could be felt. A loud bruit, maximal in systole but extending throughout diastole, was heard over the area. The thyroid gland was just palpable. A small gland was felt above the outer third of the left clavicle. There were enlarged glands in both axillae, and the tip of the spleen was palpable. Further questioning elicited the following story:

Six years ago he was riding on the top of a loaded haycart. The man leading the horse foolishly ran the wheels out of the track and the cart heeled over at a precarious angle, throwing the patient into the air. He landed on the prongs of an upturned pitchfork, which transixed his neck, entering on the right side and coming out at a slightly higher level on the left. He was intensely dyspnoeic, but his distress was relieved immediately the fork was withdrawn. There was little bleeding and the neck swelled greatly. At hospital he was given A.T.S. and the wounds were dressed without exploration or suture. After three days he was returned home. He spent the next two weeks resting, most of the time in bed. When helped to a sitting

position he was fairly comfortable, but could not raise himself unaided. There was much bruising, but the swelling subsided in about a fortnight and he returned to work a week later. The symptoms of which he now complains started a few weeks later, and have continued without much change ever since.

Investigation in hospital revealed no radiological abnormality in the chest or neck, and barium swallow was normal. Direct laryngoscopy disclosed nothing unusual. While under observation he had several attacks of malaise, with pain and throbbing in the neck, and, during one of these, fever up to 101°; there was slight generalized glandular enlargement and the spleen was palpable. In this attack the W.B.C. numbered 10,425 per c.mm., 54% of them polymorphs and 37% lymphocytes. No other febrile attack occurred, and though there was increased pulsation on the left side of the neck no definite swelling could be made out. Blood culture on one occasion showed haemolytic *Staph. albus*, coagulase-negative, thought to be a contaminant. The sedimentation rate was normal. Biopsy of the supraclavicular gland showed no abnormality and was sterile on culture.

COMMENT

The nature of these attacks could not be elucidated, as operation was considered to be unjustified in view of the mildness of the observed attacks. The patient was given a full course of sulphathiazole, but it is doubtful if this influenced the condition. He gave a history of symptoms suggestive of fever in previous attacks, but it is uncertain if it was a usual accompaniment. The fever in hospital may have been due to a coincidental infection. It was considered possible, however, that an infective process was associated with an arteriovenous communication comparable to the infective endarteritis seen in cases of patent ductus arteriosus. Apart from one possible contaminated blood culture, however, the blood was repeatedly sterile. It would appear that an arteriovenous aneurysm involving probably the superior thyroid artery was the basic pathological condition, and that some transient disturbance of the circulation in this region, due perhaps to thrombosis or embolism, resulted in an engorgement of collateral vessels. This might explain the attacks of swelling of the neck.

I wish to thank Col. J. L. Hamilton for permission to publish this case, and Dr. R. Arden Jones for assistance in its preparation.

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Intravenous Infusions in Infancy

The provision of adequate fluid is probably the most important therapeutic measure in infancy. In cases with persistent vomiting fluid must be given parenterally, and there are several methods from which to choose, the intravenous route being the method of fewest limitations. The following modification of the Spivek method has been found to be simple and rapid:

A splint is strapped to the lateral aspect of the foot and tied with tapes or bandages to the side and end of the cot. About 0.5 c.cm. of local anaesthetic (novocain or planocaine) is injected over the great saphenous vein, which, although it may not be seen or palpated, is constantly found lying anterior to the internal malleolus. A transverse incision about 1 c.cm. long is made anterior to the malleolus and the subcutaneous tissue exposed. A curved cutting or intestinal needle is inserted at one end of the incision and the point brought out at the other end. The concavity of the needle now contains the vein lying in the subcutaneous tissue. By holding the two ends of the needle between the left index finger and thumb the vein can be dissected out. When it has been isolated the curved needle is threaded with catgut and drawn through. By dividing the catgut at the needle two pieces are left lying under the vein. At this stage, before the vein is ligatured or opened, the drip apparatus should be set up and tested, because any delay later may cause clotting in the vein. An incision in the upper wall of the vein is made with fine scissors or a scalpel, and one ligature is tied distal to this incision. A blunt bevelled needle is inserted in the vein and tied in by means of the other ligature. The drip apparatus is connected to the needle and the flow started. The choice of fluid is a matter for the individual case. Often it is found that the fluid will not flow, particularly in very small or premature infants. The introduction of 10 to 20 c.cm. of saline under pressure from a syringe usually dilates the vein sufficiently to allow a free flow.

The advantages of this method are that it is quick, simple, and requires very few instruments, all of which can be found in any ward or doctor's bag. The instruments required for cutting down upon and entering the vein are a 1-c.cm. syringe, one scalpel, one curved needle, and a ligature (linen thread in an emergency). Aneurysm needle, dissecting forceps, conjunctiva tissue forceps, or even fine scissors are unnecessary.

It is important that the fluid should not be given too quickly. A simple rule is to infuse as much fluid intravenously as the infant would be given by mouth ($2\frac{1}{2}$ oz. per lb. body weight): 5 to 8 drops a minute from a drip chamber is equivalent to 15 to 25 oz. a day.

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