OBSERVATIONS ON THE USE OF PYRIFER.*

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THE use of inoculation malaria as a method of pyretotherapy still involves a relatively high figure of mortality and has other drawbacks. For example, there are the difficulties in propagating the culture, the loss of time entailed by the periods of incubation and removal of the fever, the uncertainty whether the inoculation will be successful, and the impossibility of a simultaneous administration of arsenical preparations; further, the fact that the treatment cannot be repeated satisfactorily, together with the occurrence of splenic and hepatic complications. A method of inducing pyrexia that promises freedom from these, at times, irksome conditions is therefore worthy of trial.

Pyrifer is a preparation produced from killed bacteria of the *coli* group, and is put on the market in seven different strengths, ranging from 50 million (strength I) to 5000 million (strength VII) bacteria per c.c. It is administered by intravenous injection in increasing doses, commencing with 25–50 million. The further increases in the dose depend upon the individual reaction of the patient. Paravenous injection does not involve any injury, but should be avoided on account of the insufficient fever induced. It is recommended that the ampoule be well shaken up before injection, as by this means the active ingredients are mixed uniformly.

Following the first two or three injections the attack of fever falls by lysis, with a second, but lower, rise of temperature, so that the complete recovery from the febrile condition only takes place after twenty-four to forty-eight hours. In one case the temperature took four days to fall to normal after the first injection. No further injection should be given until the temperature has returned completely to the normal.

After the third injection of pyrifer the regular typical fever rhythm appears.

Within ½–1 hour after the injection a sharp increase of temperature takes place, usually with a rigor, reaching its highest point after 2–3 hours and returning to normal within 4–8 hours.

The full course in the series to be described later has been 12 attacks of fever. The injections have been given on alternate days, and it has been possible to produce regular attacks of fever of approximately equal temperature

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by the administration of increasing doses, and to adapt the height of the fever to the physical condition of the individual patient.

The main accessory phenomena of the fever observed were headache and vomiting, but these may be avoided to a great extent by slow injection and the giving of the pyrifer with the patient in a fasting condition. In cases where these symptoms occurred considerable benefit was observed to follow the exhibition of luminal. Apart from these symptoms in a few cases, for the most part the injections were very well borne by the patients. After the subsidence of the fever the patients soon began to feel quite well again, and on the intermediate days, when free from fever, they were able to remain out of bed.

The patient's weight was usually reduced slightly by the treatment, but compensation occurred rapidly. In some cases the weight was found actually to be increased at the end of the course of treatment.

Patients in poor health need not be excluded from this form of therapy, and I have been very much impressed with the way in which this type of patient, supported by cardiac tonics, has borne the pyrexia. Two of the patients were in an exceptionally low state of health, but apparently were not affected adversely by pyrifer.

The effect of pyrifer on the blood picture has shown in two phases. Firstly, during the fever, a leucocytosis, with increased mononuclear cells, a shift to the left of the Arneth count, and a corresponding fall in the lymphocytes; secondly, with the fall in the fever, a fall in the leucocyte count and a relative increase in the lymphocytes.

In giving the results following pyrifer therapy, I will first show the findings in cases of general paralysis.

During 1933, 15 cases were given pyrifer, and of these 3 had already been given inoculation malaria before admission. The only selection made in these cases was that, with the patients who were considered too feeble to undergo malaria, pyrifer was given. Thirteen patients were inoculated with malaria during 1933. Many of those treated by pyrifer were very advanced cases, as can be judged by the fact that 5 of the 15 died from general paralysis in from 2–8 months after treatment without having shown any apparent reaction to the therapy. Of the 10 remaining, 2 have shown no mental improvement, 2 showed improvement (one an apparently complete mental recovery), but subsequently relapsed to some extent, one showed improvement, but died from lobar pneumonia 8 months after treatment, 3 showed considerable improvement and 2 have been discharged from hospital.

I should not like you to gain the impression that the high death-rate in this series is in any way due to the action of pyrifer; it merely shows the advanced state of these patients. The 5 patients who died from general paralysis were given pyrifer because, on account of their general condition, I did not feel justified in risking the use of malaria.

The total figures, then, for pyrifer treatment during 1933 may be stated as

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15 cases, with 6 patients improved, or if one excludes the advanced patients, 10 cases with 6 improved.

Of the 13 patients inoculated with malaria, 1 died less than a month after the inoculation, 5 showed no improvement, 1 showed improvement but relapsed, 3 showed slight improvement, 2 were discharged (1 to care of friends—improved), and the remaining case, sent in as a voluntary patient, left in a worse state than on admission. This last patient was in the hospital just over 3 months from the date of inoculation, but became incapable of volition. The total figures for malarial treatment during 1933 may then be stated as 13 cases, with 5 improved.

From these records it is seen that the comparison of pyrifer with malaria is, in improvements, 6/15 to 5/13, but in making the proportion I have obviously erred in favour of malaria. If one gives 3 points for discharge, 2 for considerable improvement and 1 for improvement, the figures would be: Pyrifer 15 cases, 13 points; malaria 13 cases, 9 points.

The low percentage of discharges in both series is striking, but is, I think, due to the type of cases admitted to this hospital.

The total figures for the malarial treatment of general paralysis in this hospital from February, 1928, to January, 1933, are: Cases 67, died under treatment 15, total deaths 28, discharged 11 (2 since readmitted), improved 2.

So far this year 7 general paralytics have been treated with pyrifer, of which number 5 have but recently finished the course. As the beneficial effects of pyrifer usually take about 3–6 weeks to appear, it is difficult to assess fully the results in this series. One patient was in a very advanced stage, with a large pressure sore over the sacrum on admission, and after 11 injections he developed convulsions and later died. Of the remaining 6, 3 are showing some signs of improvement.

The fever therapy in all cases, malaria and pyrifer, has been followed by courses of anti-syphilitic treatment, viz., tryparsamide and bismostab.

The next series to which I wish to direct your attention is that showing the use of pyrifer in cases of schizophrenia.

Fifteen cases have finished the course of treatment more than a month ago, whilst 6 have only more recently completed the therapy.

Of the cases referred to, all except two were recent admissions. One has been discharged and another discharged to care of friends. I have seen both of these patients fairly recently at a clinic, and both are maintaining their improvement. One, a voluntary patient from the probation officer, improved somewhat, then relapsed and later left the hospital. Five have shown some improvement and 7 have shown no change. Of the 6 more recent cases, 3 have so far shown some improvement.

I must point out that the first injection of pyrifer given to any of these patients was on June 4, 1933, and hence it is far too early to form any conclusions as to the permanency or otherwise of the improvements. The

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improvement has shown itself in better behaviour of the patients, the appearance of ability and willingness to work and an amelioration of the mental symptoms.

I should like to illustrate this series with a short account of two cases. One of these patients, æt. 20, was admitted on July 2, 1929. He took no interest in his surroundings, refused to converse or even answer a question and would not comply with the simplest request. Without any apparent cause he became excited and violent. He was faulty in habits. On June 4, 1933, when pyrifer therapy was commenced, he was in a stuporose condition, would not speak, and required spoon-feeding and every attention. His habits remained faulty. A month after treatment he would feed himself if somebody touched his hand or body. He required touching for every step he took or every mouthful he ate. Later he became able to feed himself without the magic touch, and at the present time, although his appearance is apathetic, he does everything for himself, works very well in the ward and occupational therapy class, plays badminton, and takes part in the physical exercises class. His habits are clean. He can appreciate jokes or anything said to him. He is able to speak, though always in a whisper, and during inspiration only.

Another case I should like to mention is that of a voluntary patient, admitted on January 13, 1934. He said that he had two brains, could not concentrate and could not work, as something seemed to stop him all the time. He was very introspective, and showed no interest in his surroundings. He was given a course of pyrifer injections. He has now lost the idea of the two brains, is a very good worker, and has become an enthusiastic cricketer for the patient's team.

I have also given pyrifer to two cases of paraphrenia, one case of chronic mania, one case of insanity with epilepsy and one case of alcoholic pseudo-paresis.

Of the cases of paraphrenia, one was a recent admission and one a chronic case. The recent case has shown an improvement, but there is no change in the chronic case. No improvement was observed after pyrifer in the case of chronic mania. The case of alcoholic pseudo-paresis was a patient in an extremely low state of physical health. He showed no improvement. In this case pyrifer was given by request as a last resort, and the manner in which this feeble patient bore the pyrexial attacks without apparent ill-effect was very striking and unexpected.

I gave pyrifer to the epileptic case because I have frequently observed the amelioration of fits in epileptic patients suffering from pyrexial illness. In one case which I remember vividly, an epileptic patient developed an empyema. Her fits stopped. The empyema was drained and her temperature subsided, but the fits did not recur whilst pus was present. When the pus ceased to flow the fits recommenced. In the case treated by pyrifer the fits averaged 32 every three weeks for several three-week periods before treatment, 16 in

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the three weeks of pyrifer treatment and 30 and 37 in the subsequent three-week periods.

I am cognizant of the fact that the number of cases fully treated so far, viz., 47, is far too small to form any very satisfactory conclusions. In addition sufficient time has not elapsed to ascertain whether or not the improvements are permanent. From my short experience it would appear that we have in pyrifer a valuable therapeutic preparation which, if the results are permanent, will compare favourably with malaria, or at any rate will provide us with a useful, handy and convenient alternative.

As in malarial therapy, the way in which pyrifer acts is still unknown, but no doubt the two therapies are closely allied in their mode of action. It would appear that pyrifer has certain advantages as compared with malarial treatment, as it avoids the introduction into the patient's system of a serious infectious malady which taxes his strength to the utmost. The height of the temperature can be readily controlled, and this makes it possible for the treatment to be applied to old and feeble patients. It is borne extremely well, and is comparatively free from danger. There is no pain following the injection, as in the case of preparations of sulphur in oil. A further advantage is that pyrifer can be combined with specific anti-syphilitic treatment introduced during the fever therapy, and I understand that it can be repeated as often as desired. Finally, one is able to arrange the time of the pyrexia, so that, for instance, when an injection falls due on the patient's visiting day, one can give the pyrifer early and so allow the patient to enjoy and appreciate fully the visiting period—a small point perhaps, but one which is beneficial to the well-being and happiness of the patient.

In conclusion I wish to express my thanks to Dr. Blair for his encouragement and kind permission to publish this paper, and to the members of the nursing staff, who have given me their assistance and enthusiastic co-operation.

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