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IV

DISCUSSION

DR. P. H. MANSON-BAHR remarked that Professor Warrington Yorke could only regard clinicians as poor observers in drug treatment, but he, the speaker, stood there as a clinician, and as such he wished to speak, and perhaps he would be forgiven if he said things which were not in accordance with the views which had been put forward so ably. Not everyone could hope to have the wonderful grasp of this intricate subject which Professor Yorke had; for he did not know anyone so fitted to clarify fogged brains on the subject as Professor Yorke.

All men were not mice, any more than all women were cats, and it was impossible, unfortunately, to generalise too closely from happenings in mice of what was likely to happen in men. One thing which did not happen in mice but did happen in man was drug idiosyncrasy—a very real thing. Some people were absolutely intolerant to quinine—he was not referring to hysterical women in the tropics—but genuine cases. The same could be said of emetine and plasmoquine idiosyncrasy. For several years he had held that there existed such a thing as drug-resistance in tropical parasites; he had published sixteen cases of trypanosomiasis in Europeans in which it had been shown that if these cases were treated heartily and with sufficient doses in the early stages of the disease, whether they were treated with non-arsenical compounds or with tryparsamide, if treated early and heartily, they were cured. He had quoted cases in which complete cure had seemed to have been effected, on 3 gm. of Bayer 205, in one week from the manifestation of the infection. The ideal method was to give the largest tolerable dose, for once a relapse had occurred it seemed hopeless to continue with the same drug. He had had one case of Rhodesian trypanosomiasis who was given large doses of Bayer 205 for a year, and yet died with more trypanosomes in his blood than at the beginning of the treatment. The most dramatic case he had ever seen was the first patient injected
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in London with Bayer 205. That man had been under his care two and a half years at the end of the war, and during that time he had had over 500 gr. of tartar emetic, and ay 40 gm. of atoxyl and a good quantity of salvarsan, and complete cure had apparently taken place after 2 gm. of Bayer 205 had been injected. He therefore became convinced that the right method was that of the boxing ring, to use all resources for a quick knock-out; and to do this effectively he employed alternate treatments of tryparsamide and Bayer 205, because when the parasites became "fast" to one, they became amenable to the other.

With regard to amoebic dysentery, he had long been convinced that emetine-fast amoebae occurred. Eight years ago he injected a subject of relapsing amoebic dysentery with emetine in the bowel, and produced an attack of amoebic dysentery with active parasites. Then he did a series of cases which were resistant to emetine bismuth iodide apparently, and they continued to relapse on continuation of this treatment until the patients said they would rather have the parasite than the "cure."

That experience led him to adopt a diametrically opposite treatment, namely, by oxyquiniline compound, which contained no alkaloidal basis. Since he had been alternating these treatments with emetine and yatren (oxyquinoline-sulphonic acid) during the last seven years, he had not had a relapse in a case of amoebic dysentery. He might be asked how he could prove that statement. It was difficult of proof, because it was not easy to follow cases up; but he had had cases of amoebic dysentery which had lasted forty years, and they had written to say they were permanently cured; certainly none of them had returned to him for further treatment.

He had noted that this method of alternating treatments had been extended to the relapsing fever spirochæte.

The last magnificent piece of work of Professor Warrington Yorke was an epic, and showed the value of the aeroplane as an adjunct to modern science, and had produced a very disturbing piece of evidence. Natives in the Belgian Congo had been systematically injected with tryparsamide over a territory several thousands of square miles in extent, and Chesterman had said it was difficult now to find a case of fresh infection of trypanosomiasis in
the Congo which had not been injected with tryparsamide. That the property of arsenic-resistance (an acquired character) could be transmitted through the tsetse fly was a very disturbing fact. It would be well in future to inject these natives alternately with arsenical and non-arsenical drugs.

He was not in a position to say much about syphilis, because he held, with Dr. Hanschell, that this disease was rapidly becoming so rare that extensive observations could not be made on it. But he had a case a good many years ago of syphilitic ulceration of the rectum which appeared to be drug-resistant, and Dr. Hanschell advised the speaker to give him protein shocks. That was done, and he then suddenly became non-drug-resistant, and the ulceration healed up, and he was now a perfectly healthy man. He would like to be told what this mysterious process of protein shock can do in respect of susceptibility to drugs in the human being.

Dr. H. M. Hanschell said he was competent to speak only as a clinician who had listened to Professor Warrington Yorke, and had read his work with pleasure, and that grateful instruction which became at once cogent for clinical work.

In syphilis, resistance to treatment might one day be shown, in some cases, to be due to resistance of the spirochaete itself to the particular drugs used. Meantime, it was certainly due, in other cases, to the site of the spirochaete: so that the drug never reached the parasite, or did not reach in effective quantity.

For example, were the spirochaete on the brain side of the choroid plexus the only known spirochaeticide which could reach it was tryparsamide. All the other drugs used in treatment of syphilis failed to get through the choroid plexus; and this perhaps had been too well known for the failure of those drugs in syphilis of the central nervous parenchyma to be put down to any resistance of the spirochaete itself, so located, to those drugs. It was, however, generally assumed that there could be no other site in the human host walling off the spirochaete from the drug. Against that easy assumption he would put his clinical observation of a case of chancre redux from which *Sp. pallida* was demonstrated. When first observed, the lesion was large and very hard, and the serum was, and remained, W.-negative. It required
two months longer continuous treatment than was necessary with other sero-negative chancres with the same drugs, doses and intervals between doses, before the chancre had disappeared to vision; and then the patient broke off treatment with still a small palpably hard disc in the post coronal sulcus; to return four months later, denying any interpolated coitus, and presenting a rather large hard chancre on the identical site. *Sp. pallida* was again demonstrated from the chancre and the serum had become W.-positive. The conclusion seemed warranted that that small disc of granuloma had still sheltered spirochætes; and that the dense sulcal granuloma had been comparatively impervious to the drugs. The histologist insisted on the identity of the tissue structure of the chancre granuloma with the granuloma harbouring spirochætes demonstrable in other and unobservable parts of the human host; it was therefore rash to assume that only on the glans penis could there be a granuloma comparatively impervious to drugs.

Furthermore, a very rapid elimination of the drug by some patients, thus preventing the drug reaching the parasite in sufficient concentration for sufficient length of time, could account for the lack of response to treatment; and different rates of elimination of anti-syphilitic drugs had been demonstrated in human beings.

In this connection he would mention the failure to cure or even relieve symptoms in kittens infected with *Entamoeba histolytica* by emetine—a drug effective for that infection in man; a difference accounted for by the very rapid elimination of emetine through the kitten’s kidneys. He had had cases whose resistance to treatment might perhaps have been claimed as due to drug-resistant spirochætes, but for the fact that collateral cases infected with the same strain, and in one instance a case infected by a patient during a clinical relapse after much treatment, all responded well to those same drugs and dosages which had given poor results in the resistant cases. With many other clinicians he had observed satisfactory response after protein shock to the same therapy that had previously failed. He suggested that in some unexplained way protein shock rendered a lesion more permeable to the drug and the host’s antibodies. It was discreditable to postulate drug-fast spirochætes when all that had been detected was that the syphilitic patient
had shown poor clinical response to a therapy that usually evoked a good response.

Other protozoa besides trypanosomes had been made drug-fast. Experimenters had made strains of Entamoeba histolytica fast to emetine, and to acriflavine. He did not know the composition of emetine, but acriflavine was declared to have two benzene radicles. The benzene-fast trypanosome, Professor Yorke had told them, showed no morphological change. Dr. Muriel Robertson had experimentally produced a strain of Bodo resistant to acriflavine, and this resistant strain showed a definite measurable morphological difference from the original non-acriflavine-fast stock, and both morphological difference and acriflavine fastness bred true and constant. So now they got Darwin's hypothesis of the inheritance of acquired characters proved true after all, and Weisssmann's long overruling denial of it gone by the board; and the politicians would get to know of this with dire results to the income-tax payer who would be made to provide homes fit to make heroes to breed V.D.-fast democrats.

Colonel E. T. Burke, D.S.O., said he had very thoroughly enjoyed Professor Warrington Yorke's important and helpful paper. Members of the Society were particularly interested in that gentleman's work on trypanosomes and their behaviour towards organic arsenicals, especially the aromatic series, and particularly how far that work had a bearing on the treatment of syphilis in the human being. He was convinced that Professor Yorke's researches had a very practical application to the therapy of human syphilis.

In considering resistant syphilis, there were two factors to bear in mind; first, resistance in the parasite, secondly, resistance so far as it affected the patient; and what had to be answered in any particular case of resistant syphilis was whether that resistance lay in the parasite, or whether it was a case of drug inertia on the part of the patient, or was it both. It had been definitely shown that parasitic drug resistance was an unlikely occurrence, as far as syphilis was concerned, however likely it might be to occur in the case of other parasites. One great point of difference was that the parasite of syphilis only extended to the human host, whereas in the case of other parasites one had to deal with non-human phases as well. And, as
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far as he could see from the experimental work and from clinical observation, there was no real evidence to show that drug-resistance existed in the Treponema pallidum, or could be caused in it. Some work was done by Fletcher with regard to alleged resistant malaria in the Federated Malay States; and he found that in such cases where the parasite was considered to have become quinine-resistant the patient either had not received the quinine at all, or had vomited immediately after it was given. In Findlay's "Recent Advances in Chemotherapy" it was stated that in regard to avian malaria two French workers found that quinine-resistance in a parasite, though possible, was improbable.

The speaker had never seen a case of resistant syphilis, nor had he read of one in which it could be shown that there was any element of parasitic resistance. The alleged instances of that broke down on critical examination. He agreed with Professor Yorke that such explanations of parasitic resistance with regard to syphilis were too often produced as an easy way out of a difficulty. That explanation was used as a screen to hide the results due to inadequate treatment, or bad management of a case. Still, it was prudent to admit the bare possibility of the Treponema pallidum being susceptible of developing arsphenamine-resistance, and it was obvious that the parasite could only develop such resistance while within a patient who was being treated by arsphenamine. When resistance developed, it was not the fault of the drug, but of the method in which it was used. Therefore there were only two alternatives presented to prevent arsphenamine-resistance: either not to use the drug at all, or simply to use the drug in such a way that such resistance would not occur. That meant there must be a particular method by which resistance in the parasite was most easily produced.

Professor Yorke's work showed clearly that the optimum conditions which produced resistance in a parasite, especially with regard to trypanosomes, were by exposing them to the highest concentrations of the drug which just failed to kill the parasite. He (Colonel Burke) interpreted that to mean that the practice of giving large doses of arsphenamine at long intervals between the doses was the easiest way of encouraging arsphenamine-resistance, if the parasite of syphilis was capable of
developing such. On that account his practice was to treat syphilis by small doses at very short intervals.

In 1930 he started giving two doses of 0·3 gm. of stabilarsan in each seven-day period instead of one dose of 0·6 gm. in the same time. The effect was not only to discourage arsphenamine-resistance, but also that one was able to give a higher total dosage in a constant time-period. Such a patient was better able to tolerate much higher dosage than if the drug were given in a single weekly dose. The lesson was learned that no single dose exceeding 0·6 of a gramme should be given, and that was borne out by a recent observation by Jadassohn that in Germany if a larger dose than 0·6 gm. was followed by a complication, then there was material for an official inquiry into the case. If the optimum dose for a patient in a week is 0·6 of a gramme, one could give two doses of 0·45 of a gramme each, making 0·9 gm. in all; or one of 0·45 and one of 0·3, which would equal 0·75 of a gramme, in each case a greater amount than would be tolerated in a single dose.

A further point is that many cases termed arsphenamine-resistant are not so at all; in many cases it is an apparent, not a real, resistance. The type he was referring to was that in which there were recorded early tertiary manifestations, i.e., occurring within six months of the appearance of the initial lesion. Recently ten cases were described in which these things happened during the active treatment of the disease; and in those one must realise that though, in point of time, a case was only six months old, in point of pathological fact the case was six or more years old; and hence the therapy which one would expect would meet with a satisfactory response in early syphilis did not have such a response in a late case after these tertiary manifestations had appeared. Therefore the drug-resistance in these cases was more apparent than real.

Another point was the following: His former chief-assistant (Dr. F. W. F. Purcell, who had read a paper before this Society) pointed out, from an analysis of cases in his (Colonel Burke's) clinic, that relapse was particularly likely to occur when there was a gap in the therapy between the sixth and twelfth week from commencing treatment; and it had been found that by cloaking that gap by means of mercury no change was made in respect
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of liability to early relapse. The administration of mercury by itself was equivalent to default in the treatment.

The conclusions he had reached in regard to resistant syphilis were as follow: (1) that resistant syphilis was more frequently seen in women than in men, and in the former between the age of puberty and the menopause; (2) that drug-resistance in the parasite was a possibility, but was highly improbable, and that the only means, so far as he knew, of diagnosing that the parasite was drug-resistant was by transferring it from a patient suffering from arsphenamine-resistant syphilis to a rabbit, and investigating the parasite for drug-resistance in that rabbit. Whenever that had been done, it gave a negative result.

Resistant syphilis seemed to be due to one of three things: (a) the inadequate treatment of early syphilis, especially when there was some fault in the therapy in the first twelve weeks; and in those cases it was a pseudo-resistance; it was a condition of early tertiarism; (b) there might be a condition of primary drug inertia on the part of the patient, an inability on the part of the body of such a patient to use the arsphenamine and bismuth employed; there must be something lacking in such a patient's metabolic make-up; (c) there might be a condition of secondary drug inertia, in which this condition was acquired, the result of faulty dosage, or a too-long continued use of one particular drug.

As far as he could see, the question of resistant syphilis was one in which the fault was not in the seed, but in the soil. When the primary resistance was due to a metabolic fault on the part of the patient, it meant that though one might give a patient arsenical drugs by the gallon, he was simply unable to use them. When Dr. Semon demonstrated a cure of resistant syphilis to the Society some years ago, Major Doble mentioned that he had seen two or three cases in which the basal metabolic rate of the patient was very low, and that had been the speaker's experience in his own clinic. Mention had been made of treating these cases by protein shock, by fever therapy, by calcium thiosulphate, or by thyroid extract, with the object of getting the patient to become a normally reacting subject to the drugs. In many of these cases, though active clinical signs might be present, the
serology was negative. Secondary drug inertia was induced by wrong therapy, and one expression of it was serological-fastness.

A point made by Professor Yorke was that in order to get rid of drug inertia it was of no use to continue with the same drug, or the same type of drug to which the patient showed resistance. The fault lay with the patient. That was borne out by the leucocytic reaction, described by Gouin. If a blood count was made before and after injection of anti-syphilitic agents, and the injection was found to cause leucopaenia, it was an indication of drug inertia; and an agent which caused leucopaenia in a patient was futile with regard to the treatment of his syphilis. A leucocytosis indicated that the patient was responsive to the drug.

He had very much appreciated the opening paper, which ought to give the death-blow to the idea that the parasite of syphilis was becoming arsphenamine-resistant.

Dr. Anwyll Davies said he had very much enjoyed Professor Warrington Yorke's paper; his researches had given him, the speaker, a great deal to think about. He had the greatest respect for the Professor's experiments, but thought, as a clinician, that the spirochaete did become arsenic-resistant, though it was true that a case which could be labelled arsenic-resistant was a rarity; he had seen only one such case which he could be sure of, that of a strong man who had been treated in a clinic in London with very small injections over a period of seventeen months. He became progressively worse, until he entered the speaker's clinic looking like a skeleton, a picture of malignant syphilis. He had an eczematous rash. He was given bismuth, and in two or three weeks he seemed a different being. That he regarded as a true case of arsenic-resistance. Though so few cases of the kind were seen, they must be borne in mind, and when they occurred they must be dealt with accordingly, because, from the clinical point of view, there were two features which indicated the possibility of the spirochaete becoming resistant. The first was that the best results were obtained when the patient received the most efficient and most thorough treatment at the outset of the disease. The second was that one's failures, the relapses and recurrences, were due to the fact that the patient had had inefficient treatment at the commencement of the disease,
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i.e., the spirochaete had to some extent probably become resistant to the arsenobenzene. They were certainly facts, and their clinical importance was great. At the Whitechapel clinic the drugs were alternated during each week. If neoarsphenamine was used at the beginning of the week, that drug was alternated by administering sulpharsphenamine towards the end of the same week. So that two different arsenical preparations were exhibited each week, bismuth being given at the same time. The results were very satisfactory.

Dr. LLOYD also added his appreciation of Professor Yorke’s paper, and of the remarks of the other speakers. He wished to make a few remarks on the fusoo-spirillary infections in the mouth called Vincent’s angina. In the last few years he had been impressed by the frequent occurrence of Vincent’s organisms in the mouth when mild bismuth stomatitis was present. In most cases of stomatitis, particularly if superficial erosions were present, the Vincent organisms could be recovered with ease. The accepted treatment for Vincent’s angina had been one of the arsphenamines, which had been in use for years as a local application, with good results, those results being improved by intravenous therapy. In most of his own cases the infections had appeared in patients who had had considerable arsenic, a fact which caused him a good deal of surprise. The condition was a profuse growth of Vincent’s organisms in devitalised tissues in a patient whose tissues were fairly full of arsenic. He had not treated those cases immediately with further arsenicals, chiefly because of the mouth condition. He had noted that after these lesions had healed up one could recover the Vincent organisms from the gingival margins, even after arsenical treatment had been renewed. He did not know whether true arsenic-resistance had been suggested in the case of Vincent’s organisms, and he asked Professor Yorke’s opinion on this point.

Colonel L. W. HARRISON said the hour was very late, and his remarks would be brief. He hoped that Professor Yorke’s paper would put an end to the loose talk about arsenic-fast spirochaetes which seemed so prevalent. Professor Yorke had shown, as before, that drug-resistance was transmissible and, this being the case, if there was such a thing as salvarsan-resistant S. pallida, we should expect resistant syphilis by now to be rife in the country,
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seeing that in many places clinicians had been treating syphilis on the very lines calculated to produce drug-resistance. Many workers treated throughout, or at any rate for a number of weeks, with individual doses far below those calculated to cause the disappearance of spirochaetes from the serum of such superficial lesions as chancres.

On the question of individual dosage he would like to remark that the finest immediate results he had ever seen in early cases were obtained by a course consisting of 0·6 gm. "606"; 5 × gr. 1 Hg.; 0·6 gm. "606"; 5 × gr. 1 Hg.; 0·6 gm. "606," given in a period of approximately nine weeks. That course had produced definitely better immediate results than had one introduced subsequently consisting of 8 × 0·3 gm. "606," given in approximately a month with corresponding mercury. In the one case, therefore, 1·8 gm. "606" in large individual doses had effected more than 2·4 gm. "606" in smaller ones. He thought that workers ought to have regard to the dose which caused the disappearance of spirochaetes from the serum of early lesions. Nothing much in this respect could be expected from a smaller dose than 0·45 gm. "914," and he might remark that 0·6 gm. Stabilarsan was not so effective immediately as was 0·45 gm. "914."

Professor WARRINGTON YORKE, in reply, said that Colonel Burke misunderstood him when he said that he, the speaker, had sounded the death-knell of arsenic-resistance in syphilis. He was sorry if he had done that, as he had tried to make it plain that syphilis was a subject he knew nothing about. If syphilis was becoming drug-resistant it was curious that the fact was now not clearly manifest; because the causal organism of syphilis had not even to pass through an intermediate host, as had the trypanosomes; it was transmitted directly from man to man. He was not quite sure, however, whether there might not be a fallacy in this line of reasoning; it was possible that the parasite might become resistant at later stages of the disease when much treatment had been administered, and long after the patient was likely to transmit the infection to others. This might explain the existence of isolated resistant infections.

Colonel Burke had used the expression "adequate treatment," and it was one the speaker had frequently heard used; but he had never understood what it meant.
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His conclusion was that it was the treatment carried out by the man who used the expression. Dr. Manson-Bahr talked of "Hearty treatment"—an original expression, which left no one in doubt as to its meaning. There was nothing material as between Dr. Manson-Bahr and himself; their results were much the same. He, Professor Yorke, had been using a "blunderbuss" method for years in the treatment of amoebic dysentery, and his results were excellent. The difference between Dr. Manson-Bahr and himself appeared to be this: Dr. Manson-Bahr attributed the failure with emetine to the fact that the parasite had become emetic-resistant, whereas he, the speaker, said he did not know—there might be some other explanation. It was in his opinion essential that one should distinguish clearly between resistance to treatment and drug-resistance on the part of the parasite.

The meeting concluded with a vote of thanks to Professor Warrington Yorke.