increased serum F.D.P. levels in women with clinically significant menorrhagia, as compared with those in women without abnormal menstrual symptoms. Further studies being undertaken indicate that raised serum F.D.P. levels found in women with menorrhagia are often associated with increased levels of fibrin monomer complexes in the blood. Thus raised serum F.D.P. levels in women complaining of menorrhagia may be a manifestation of exaggerated intravascular microcoagulation associated with secondary fibrinolytic activity.—I am, etc.,

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¹ Hallberg, L., Högdahl, A. M., Nilsson, L., and Rybo, G., *Acta Obstetrica et Gynaecologica Scandinavica*, 1966, 45, 320.

Serum Hepatitis Hazard in Biochemical Control Sera

SIR,—We have found hepatitis associated antigen (H.A.A.) in two samples of commercially produced human serum used as controls in biochemical tests. These are Hyland Q-Pak Chemistry Control Serum II batch no. 3655 M022A2 and Warner Chilcott Versatol Diagnostic Reagent batch no. 0089027. The antigen is present in high titre as shown by countercurrent electrophoresis, electron microscopy, and by gel diffusion. Identity can be shown in the last test with known positive antigens.

We have since tested several other batches of these manufacturers' products and 50 other samples of similar products with negative results.

In view of the obvious hazard to laboratory staff we strongly recommend that all such material should be tested for H.A.A. before use.—We are, etc.,

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Antibiotic-resistant Gonococci

SIR,—In your very useful leading article (18 December 1971, p. 696) you comment on the present halt in the increase of resistant gonococci in Britain and warn that this respite is likely to be only temporary. If this be so now is the time to take action to prevent a situation developing such as you describe in other parts of the world. But what action? We agree with your advice concerning treatment in the individual, but we think that more is needed. Unfortunately, however, the amount of useful advice which can be offered is limited by our ignorance.

We do not know enough about the two essential ingredients in the epidemic situation: the gonococcus and the population at risk. As to the gonococcus we could make a sizeable list of the relevant items which as yet are unknown, and as to the population it is now so heterogeneous and subject to rapid change that much we thought we knew is out of date. Clearly intensified bacteriological investigation and sociological study are called for. While awaiting these we would like to draw attention to the use of sensitivity testing not only to guide in the treatment of the individual and to monitor changes in the incidence of resistant strains but as a tool for epidemiological study. If the results of penicillin

sensitivity tests are correlated, case by case, with information gained by clinician and social worker and the complete data analysed light is thrown on current epidemiological patterns and on the mechanisms of emerging resistance.

As an example of the value of such studies we refer you to our report¹ on a study of penicillin-insensitive gonococci in the Bolton area in the months just prior to the introduction of high-dosage penicillin therapy in 1969. Among other observations we found a significant preponderance of insensitive strains in immigrants as compared with non-immigrants, and also an apparent preponderance of insensitive strains in younger nonimmigrant females as compared with other indigenous groups. The latter finding we thought to be evidence that many young women were being treated elsewhere than in the clinic because, that being so, referrals would be mainly of those with resistant infections.

For analytical purposes we found that a simple classification of strains by penicillin sensitivity was useful: sensitive (penicillin minimum inhibitory concentration <0.015 µg/ml); intermediate (M.I.C. 0.03–0.06 µg/ml); and insensitive (M.I.C. >0.12 µg/ml). We encountered no highly insensitive strains but such a category would be desirable for strains of M.I.C. >0.5 µg/ml.

We provided evidence that penicillin M.I.C. is a sufficiently stable character of individual strains to be used epidemiologically in the way indicated. We believe that studies such as ours, on a greater scale, would provide results which would be very helpful in planning future control measures.—We are, etc.,

P. S. SILVER
W. M. DARLING

Diagnostic Clinic,
Health Department,
Bolton, Lancs

¹ Silver, P. S., and Darling, W. M., *British Journal of Venereal Diseases*, 1971, 47, 367.

Unusual Reaction to Trimethoprim in Combined Therapy

SIR,—The use of a new drug, which associates a sulphonamide with trimethoprim, represents a therapeutic advance. This drug works on two consecutive levels of bacterial metabolism, and this diminishes the risk of acquired bacterial resistance. Soon after the drug came into use various side effects were reported, the most common being skin rashes.

I should like to report the following case in which a morbilliform rash appeared to be due to trimethoprim.

A 49-year-old woman had suffered from severe asthma since 1957. In February 1968 she had a thyroid nodule removed, and since then her asthma had been worse, with frequent attacks of status asthmaticus. Immunotherapy has been ineffective. She is also allergic to several drugs: aspirin, penicillin, and aminopyrine and its derivatives.

On 22 January 1971 she became very dyspnoeic with wheezing and rhonchi, and had pus in the nose and sputum. She was put on sulfamethoxazole-trimethoprim: 400 mg/80 mg four times a day for 10 days. The therapeutic effect was good and pus disappeared both in nose and in sputum. On the tenth day a morbilliform rash appeared, localized to trunk and popliteal spaces, and she had joint pains. The administration of

the drug was immediately stopped, and I prescribed 0.25 mg betamethasone with 2 mg dexchlorpheniramine in half dose three times a day for three days. The rash and arthralgias disappeared.

This observation resembles other reported cases, but, in this particular case, an interesting fact was mentioned by the patient. Two years before, she had an identical rash after having taken bamifylline (Trentadil) a bronchodilator which has in common with trimethoprim a pyrimidine nucleus.

Several weeks later the patient could take sulfamethoxazole without any reaction, and therefore I consider that in this case trimethoprim could be considered as responsible for the rash and arthralgia.

It seems that trimethoprim is seldom responsible for skin or systemic allergic reactions, but the possibility must be kept in mind when one prescribes the very useful combination of sulfamethoxazole-trimethoprim.—I am, etc.,

GEORGES M. HALPERN

Paris

Rifampicin and Isoniazid and Liver Function

SIR,—The experience of Dr. Satinder Lal and others (15 January, p. 148) on the effect of rifampicin and isoniazid (I.N.H.) on liver function is similar in a way to my own. I have found the rise of aspartate transaminase (SGOT) not to indicate significant abnormality of liver function and have naturally continued chemotherapy with rifampicin and isoniazid. I have, however, seen hepatotoxicity in patients receiving treatment for *Mycobacterium tuberculosis* infection with rifampicin and isoniazid when this is determined by measurement of bilirubin, alkaline phosphatase, and alanine transaminase (SGPT). The first indications have generally been symptomatic. Patients with these biochemical abnormalities, especially raised alanine transaminase, have generally felt unwell before biochemical detection of the abnormalities. The biochemical checks are carried out before and fortnightly after starting treatment.

A review of the experience of this clinic since 1969 showed that 26 patients had been treated with rifampicin and isoniazid up to early 1971. Of that number, eight (or 30%) showed abnormality of liver function, indicated by raised bilirubin (more than 1 mg/100 ml), raised alkaline phosphatase (greater than 15 King Armstrong units/100 ml), and raised alanine transaminase (SGPT more than 40 m.i.u./ml). There was only one case of raised alkaline phosphatase alone. This was in a child of 6 years and the level was greater than 35 K.A. units. Treatment was continued without any adverse effect or any other abnormality. I have since been told that this is not unexpected in children and appears to be harmless. The alkaline phosphatase returned to normal values on cessation of therapy and the child has remained well thereafter. One case showed the bilirubin alone was raised. Here again treatment was continued and the values returned to normal eventually. There were no symptoms. In all the others there was abnormality of enzyme (SGPT) together with abnormality of either or both bilirubin and alkaline phosphatase. In these there were symptoms referable to liver dysfunction such as anorexia, nausea, and vomiting. Also,