

Relationship between rifampicin-dependent antibody scores, serum rifampicin concentrations and symptoms in patients with adverse reactions to intermittent rifampicin treatment

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Summary

Twelve patients receiving intermittent treatment with rifampicin for pulmonary tuberculosis, who had developed rifampicin-dependent antibodies were studied. Ten of the twelve patients had also developed adverse reactions to the drug at the time the study was done. After a dose of the drug, blood samples were taken from each patient at regular intervals for the assessment of rifampicin-dependent antibodies by a semi-quantitative method, and for the measurement of serum rifampicin concentrations. Clinical details of any adverse reactions which occurred were also recorded at these set times. Serum rifampicin concentrations were at their highest from 1 to 12 hr after a dose, and during this same period the rifampicin-dependent antibody score was reduced. Adverse reactions, when they occurred, coincided with the period of high serum rifampicin concentration and low antibody score. Whether or not these findings are of immunological significance is discussed.

Introduction

Rifampicin has been found to be one of the most potent drugs in the treatment of tuberculosis (Verbist & Gyselen, 1968; Gyselen *et al.*, 1969; Decroix *et al.*, 1969, 1971; Newman *et al.*, 1971; Pines, 1971), and is highly effective when given to the experimental animal on an intermittent basis (Batten, 1969; Grumbach, Canetti & Le Lirzin, 1969; Dickinson & Mitchison, 1970). Intermittent rifampicin regimens would be ideal for the retreatment of patients with resistant tuberculosis in Hong Kong because every dose could be given under full supervision. Furthermore, an intermittent regimen would be cheaper and perhaps less likely to cause adverse reactions than a daily one.

However, in a controlled clinical trial on the treatment of tuberculosis that is currently being carried out in Hong Kong by the Hong Kong Tuberculosis Treatment Services, The Brompton Hospital and the British Medical Research Council, daily and intermittent rifampicin regimens are being compared and reports of the results after

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6 and 12 months have shown an unexpectedly high incidence of adverse reactions to rifampicin given on an intermittent basis (Aquinas *et al.*, 1972; Girling, 1973). Of these, the commonest has been fever, often accompanied by chills, headache, malaise and bone pains occurring shortly after taking the drug and termed the 'flu' syndrome.

Regular serological investigations on these patients had shown that over 30% of the patients on intermittent rifampicin treatment developed rifampicin-dependent antibodies and there was a highly significant statistical correlation between the development of the 'flu' syndrome and the presence of these antibodies (Worlledge, 1973).

It was decided to study in more detail a group of patients with rifampicin-dependent antibodies in an attempt to answer two questions. First, what was the significance of these rifampicin-dependent antibodies and second, did they play any role in the pathogenesis of the 'flu' syndrome?

Material and Methods

Patients studied

Twelve patients were studied, all of whom had developed rifampicin-dependent anti-

Table 1. Age, sex and regimens of patients studied

Patient no.	Age	Sex	Regimen
1	37	M	ER7 ER1
2	43	M	ER7 ER1
3	33	M	ER1
4	51	M	ER2
5	62	M	ER1
6	32	M	ER2
7	41	M	EZR1 ER1
8	46	M	EZR1 ER1*
9	60	M	EZR1 ER1
10	59	F	EZR1 ER1
11	38	M	EZR1 ER1*
12	58	M	EZR1 ER1

* These two patients were receiving a small daily supplement of rifampicin 75 mg in addition to their once-weekly regimen.

bodies in their serum during intermittent treatment with the drug. Two of the patients were asymptomatic, the remaining ten had the 'flu' syndrome. Details of the age, sex and treatment of each patient are shown in Table 1.

Treatment given

The patients were all receiving one of the following regimens (Table 1): ethambutol and rifampicin twice weekly (ER2); ethambutol and rifampicin once weekly (ER1); ethambutol and rifampicin daily for 2 months and then once weekly (ER7 ER1); ethambutol, rifampicin, pyrazinamide once-weekly for 3 months and then ethambutol and rifampicin once weekly (EZR1 ER1).

Two of the six patients on the EZR1 ER1 regimen received a small daily supplement of 75 mg of rifampicin in addition to their weekly doses.

Methods of study

The patients were all in hospital and each was studied after an oral dose of his or her allocated weekly or twice weekly treatment. However, if reactions had already occurred and had been severe the dose of rifampicin was less than the allocated dose.

The symptoms and signs that developed after the dose was given were recorded in detail. Blood samples were taken for estimation of rifampicin concentrations and rifampicin-dependent antibody scores (see later) before the dose was given and at 1, 2, 4, 8, 12 and 24 hr after the dose.

Antibody tests

Antibody tests were done by the indirect antiglobulin method of Poole, Stradling & Worledge (1971). The results were read with anti-complement sera (anti- β IC/ β IA sera manufactured by Beringwerke). An anti-IgG serum was not used. The patients' serum was separated from the red cells within 2 hr of taking the sample and was either tested at once or frozen to -20°C and tested within 72 hr. A saturated solution of rifampicin was made up by adding the contents of three 150 mg capsules of the drug to 100 ml saline. This solution was filtered and kept at 4°C .

The anti- β IC/ β IA globulin sera were dialysed and stored at -20°C until needed for the test. Each batch of antiserum was controlled with a known positive serum to determine optimum dilution which varied from 1/30 to 1/60. The tests were read on perspex plates (WHO Agglutination trays) after half an hour. A second reading to confirm these results was done after shaking the plates and allowing them to resettle after a further half hour. The results were then scored as follows: 0 = a negative result with a perfectly smooth button of sedimented red cells surrounded by a halo of clear serum; ? = a doubtful result, with a slight graininess of the halo; $\frac{1}{2}$ = a positive but very weak result with a fine granularity in the halo and a central button that was a little more dispersed than the control; 1 = a granularity throughout the halo and a larger central button; 2 = more granularity in the halo and an irregular central button; 3 = a denser granularity throughout the peripheral halo of serum and some central sedimentation with a markedly uneven border; 4 = a complete and even dispersion of deposited cells with no central sediment.

Saline was substituted for rifampicin solution as a control with all sera and care was taken to see that there was no difference in pH activity. Antibody titres were not done and no attempt was made to reach the end point of agglutination. Some of the tests were done with serum diluted in fresh normal serum and the details of the dilutions are given in Table 2.

Serum rifampicin concentrations

Rifampicin concentrations in the sera were measured in the MRC Unit for Laboratory Studies of Tuberculosis (Royal Postgraduate Medical School, London) using a diffusion technique. Plates were seeded with *Staphylococcus aureus* (NTCT0702) and the serum added to wells in the plate. Zones of inhibition of growth were measured after incubation for 24 hr and compared with standard concentrations of 0.02–1.28 $\mu\text{g}/\text{ml}$ rifampicin in normal human serum. The method is sensitive to 0.01 $\mu\text{g}/\text{ml}$ rifampicin (Mitchison, 1973).

Table 2. Antibody score, serum rifampicin concentrations and presence or absence of symptoms after a stated dose of rifampicin

Patient no.	Dose of rifampicin (mg)		Hours after dose											
			0	1	2	4	8	12	24	Symptoms				
1	1050	Antibody scores (undiluted serum)	3	2	2	1	1	1	4					
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	36.8	28.4	32.4	42	19.3	1.0	Fever, bone pain and chills				
		Presence or absence of symptoms	—	+	+	+	+	+	—					
2	450	Antibody scores (serum diluted 1:4)	4	3	3	3	3	3	3	Fever, chills, itching and headaches				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	28.4	22	17	22	2.5	0.2					
		Presence or absence of symptoms	—	+	+	+	+	—	—					
3	900	Antibody scores (undiluted serum)	3	0	0	0	0	1	1	Fever, bone pain and headaches				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	95.9	36.8	25	17	7.8	0.63					
		Presence or absence of symptoms	—	—	+	+	+	—	—					
4	1050	Antibody scores (serum diluted 1:4)	3	3	3	3	3	2	2	Fever, chills and headaches				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	27.2	44.3	34.7	18.9	9.1	0.2					
		Presence or absence of symptoms	—	—	+	+	+	—	—					
5	1050	Antibody scores (serum diluted 1:5)	3	3	1	1	1	?	1	Fever, chills, itching and dyspnoea; jaundice at 24 hr				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	26.7	26.7	39.2	34.7	26.7	13.1					
		Presence or absence of symptoms	—	+	+	+	+	+	—					
6	900	Antibody scores (undiluted serum)	2	?	?	?	?	?	?	Fever and headaches				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	16.5	25.5	17.2	9.8	7.6	0.2					
		Presence or absence of symptoms	—	—	—	—	+	+	—					
7	1050	Antibody scores (undiluted serum)	3	1	1	1	1	1	1	Fever and flushing; jaundice at 24 hr				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	26.7	38	32.8	34.4	19.2	7.8					
		Presence or absence of symptoms	—	+	+	+	+	+	+					
8	1050	Antibody scores (undiluted serum)	2	2	1	0	0	0	0	Fever and rash				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	0.05	22	20.6	16.2	5.6	0.2					
		Presence or absence of symptoms	—	—	—	—	+	+	—					
9	900	Antibody scores (undiluted serum)	4	4	4	4	3	4	4	Fever				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	11.4	31.1	18.6	10.3	3.9	0.6					
		Presence or absence of symptoms	—	—	—	+	+	—	—					
10	1200	Antibody scores (serum diluted 1:4)	3	2	1	?	?	1	1	Fever, chills and vomiting; jaundice at 24 hr				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	55.7	48.4	34.7	19.4	10	1					
		Presence or absence of symptoms	—	—	+	+	+	—	—					
11	1200	Antibody scores (serum diluted 1:2)	2	2	2	2	1	1	1	None				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	3.8	26.1	23.3	14.3	10.1	0.6					
		Presence or absence of symptoms	—	—	—	—	—	—	—					
12	1200	Antibody scores (undiluted serum)	1	?	0	0	0	0	?	None				
		Serum rifampicin concentrations ($\mu\text{g/ml}$)	<0.02	25	43.6	28.7	20.7	15.3	2					
		Presence or absence of symptoms	—	—	—	—	—	—	—					

Results

Table 2 shows the antibody scores, the serum rifampicin concentrations and the presence or absence of symptoms for each patient at set times after the stated dose of rifampicin. The actual symptoms experienced are given in the last column. Seven of the patients showed a change in antibody score when undiluted serum samples, taken at the stated times after the dose of rifampicin had been given, were tested. Five of the patients showed no such change when undiluted serum was used and the least dilution at which a change was observed is given and the results at this dilution shown.

Antibody scores

Antibody tests on serum taken after the dose of rifampicin showed a decrease in the strength of the *in vitro* reaction and in most cases this was associated with high rifampicin levels. In patients 3, 8 and 12 the antibodies became undetectable for some hours after the dose of rifampicin. The serum of the nine other patients all gave detectable, but weaker reactions although in some cases the serum had to be diluted before this was obvious. By 24 hr, the reactions were increasing again in seven of the twelve patients. In patients who developed the 'flu' syndrome, the symptoms tended to coincide with the time when the antibody reactions were weakest.

Serum rifampicin levels

In most patients, the serum rifampicin levels reached a peak at 1–2 hr and high concentrations were maintained for 12 hr. Even at 24 hr the levels were above the pre-dose level. However, in those patients with the most prolonged reactions (1, 2, 5 and 7) there was either a second peak at 8 hr or a delayed peak at 4 hr. Patients 5 and 7 had unusually high concentrations of rifampicin in their sera at 24 hr and both became jaundiced and showed transient rises in serum alanine aminotransferase activity. However, patient 10 who was also jaundiced at 24 hr did not have an unusually high concentration of rifampicin in her serum at that time. The lowest concentration of rifampicin during symptoms was 5.6 µg/ml (patient 8), and patients 11 and 12 attained high concentrations and yet had no symptoms.

Adverse reactions

Ten of the twelve patients studied developed the 'flu' syndrome after the dose of rifampicin was given. The symptoms lasted from 4 to 11 hr. In six patients (1, 2, 3, 5, 7 and 10) the symptoms started within 2 hr of giving the drug: in four patients (4, 6, 8 and 9) they appeared 4–8 hr after the dose, and in two patients (11 and 12) there were no adverse effects. When symptoms started soon after the dose of rifampicin they tended to last a long time. In contrast, when symptoms were delayed they tended to be short-lived.

Effects of changes of treatment (if any) on the antibodies in the serum (Table 3)

Seven of the ten patients who developed the 'flu' syndrome (1, 3, 6, 7, 8, 9 and 10) no longer had symptoms when their treatment was changed to daily rifampicin and ethambutol and the rifampicin-dependent antibodies disappeared from their sera in 2–6 weeks. Two patients (2 and 5) still had symptoms when a daily dose of 450 mg of rifampicin was given and the drug was discontinued. Rifampicin-dependent antibodies

Table 3. Presence or absence of antibodies in the serum in the weeks following change of treatment (if any)

Patient no.	Weeks										Details of change (if any)
	1	2	3	4	5	6	7	8	16		
1	+	+	+	0	0	0	0	0		Daily rifampicin	
2	+	+	+	+	+	+	+	+	+	Rifampicin discontinued	
3	+	+	+	+	+	0	0	0		Daily rifampicin	
4	+	+	+	+	+	+	+	+	+	Twice weekly rifampicin (900 mg)	
5	+	+	+	+	+	+	+	+	+	Rifampicin discontinued	
6	+	+	+	0	0	0	0	0		Daily rifampicin	
7	+	0	0	0	0	0	0	0		Daily rifampicin	
8	+	+	0	0	0	0	0	0		Daily rifampicin	
9	+	+	+	+	+	0	0	0		Daily rifampicin	
10	+	+	+	+	0	0	0	0		Daily rifampicin	
11	+	+	+	+	+	+	+	0		ER1 continued	
12	+	+	0	0	0	0	0	0		ER1 continued	

were still detectable in their sera 16 weeks later. Patient 4 had the dose of rifampicin reduced from 1050 to 900 mg and the twice-weekly regimen was continued. His symptoms disappeared but the antibodies were still detectable in the serum 16 weeks later. Patients 11 and 12 were continued on their once-weekly regimen and no symptoms occurred. The rifampicin-dependent antibodies disappeared from their sera in spite of continued treatment.

Discussion

The significance of the antibodies

The first thing that must be established is whether or not the serological reactions are, in fact, due to antibodies. They are detected by demonstrating complement on the surface of red cells, and from other studies (Worlledge, 1973) it has been shown that immunoglobulins are only very rarely present. However, the work of Sors, Sarrazin & Homberg (1972) and Worlledge (1973), shows that the reaction will not occur after treatment of the sera with 0.01 M 2-mercaptoethanol and the fraction of the serum responsible for the complement fixation comes down with the IgM fraction of DEAE cellulose. Thus, it seems likely that the complement is bound by IgM antibody.

The fact that the complement and not IgM is detected on the red cell surface cannot be due to insufficient amounts of antibody for some of the patients, for example patient 5 and the patient described by Sors *et al.* (1972) had antibodies present in high titre. The complement fixation does not occur when the patient's serum is incubated with normal red cells in the absence of the drug and therefore the antibody, if present, does not react against normal red cell antigens and presumably is not firmly attached to the red cell surface. The most probable explanation for the absence of antibody in the final tests is that it elutes from the red cells during the washing process prior to reading the test.

Previous studies (Poole, Stradling & Worlledge, 1971; Worlledge, 1973) on these antibody-like reactions have established the following facts:

- (a) they do not occur in normal persons or in persons with tuberculosis who are not taking rifampicin;
- (b) they occur only very rarely when daily rifampicin is given;
- (c) they appear in the serum of a significant number of patients taking twice-weekly (26%) and once-weekly (50%) rifampicin, mainly at the 4th–6th month of treatment;
- (d) they gradually become undetectable once the drug is discontinued.

Reactions like these would be expected if rifampicin-dependent antibodies could develop. Free antibody would be unlikely to be present in patients taking daily rifampicin because even the patient who received 450 mg of the drug (patient 2) still had detectable drug in the serum at 24 hr. However, patients taking rifampicin twice or once-weekly would have periods at which no free drug was present and antibodies could arise. In patients 11 and 12 where once-weekly rifampicin was continued, even this discontinuous dosage seemed to lead to eventual suppression of the 'antibodies'. In patients 1, 3, 6, 7, 8, 9 and 10 where the treatment was changed to daily rifampicin, 'antibodies' could no longer be detected after 2–6 weeks. Only in patients 2 and 5 whose rifampicin was discontinued and in patient 4 whose dose was reduced to 900 mg twice a week, were 'antibodies' still detectable in the serum at 16 weeks.

It is mainly the fact that there has been very little success in producing antibodies to rifampicin in animals (Dukor, Schumann & Dietrich, 1973) that prevents the complete acceptance of these antibody-like reactions as being due to true antibodies. However, it is well known that the positive antiglobulin tests produced by methyl dopa administration do not occur in animals. Moreover, phenacetin and stibophen (to name but a few of possible drugs) can produce an immune haemolytic anaemia in which antibodies, detectable by similar methods, are found. It is generally accepted that the symptoms in these patients are directly due to these antibodies, even though there is no proof in experimental animals that antibodies do, in fact, appear.

It is interesting that none of our patients developed any haematological abnormality: both immune haemolytic anaemia (Hasse *et al.*, 1971; Sors *et al.*, 1972; Lakshminarayan, Saho & Hudson, 1973) and immune thrombocytopenia (Blajchman *et al.*, 1970; Poole *et al.*, 1971) have been described in other patients and these haematological abnormalities are accompanied by similar antibodies.

The presence of the fourth component of complement as well as the third component on the surface of the red cells that react with anti-complement sera (Worlledge, personal communication) makes it unlikely that the complement could have been activated by the alternative pathway and, therefore, by means other than antigen-antibody reactions.

The role of the antibodies in the pathogenesis of the 'flu' syndrome

Antigen-antibody reactions can lead to the development of fever. Rabbits sensitized to bovine serum albumin, or human serum albumin can develop fever on subsequent challenge with antigen (Farr *et al.*, 1954; Farr, 1958, 1959). Moreover, in a study by Mott & Wolff (1966) it was shown that this febrile reaction was associated with detectable antibody in the serum of a high proportion of the animals. Furthermore, the febrile reaction after challenge could be transferred to normal rabbits by the transfusion of serum only from sensitized rabbits who had detectable antibody.

Febrile reactions due to antibody are also seen in humans. The reactions that follow

incompatible blood transfusions or transfusions of whole blood to patients with white cell antibodies are well known but in these there is destruction of blood cells. However, the reactions that follow the infusion of normal plasma to persons with absent IgA and anti-IgA in their serum (Schmidt, Taswell & Gleich, 1969; Ropars *et al.*, 1971) do not involve obvious destruction of blood cells. In these reactions, the symptoms and signs may include fever, malaise, nausea, flushing of the face, dyspnoea and bone pains and these patients have IgG anti-IgA in their serum often to a high titre. This antibody binds complement components after it has reacted with IgA and the role of complement in the causation of the symptoms is not yet clear. The activation of the third and fifth components of complement leads to the production of anaphylatoxins which could give rise to many of the symptoms.

An alternative explanation for the symptoms of the 'flu' syndrome might be that they are a direct toxic effect of the drug. Symptoms, when they occurred, were limited to the period of high rifampicin concentrations and the lowest concentration recorded while symptoms were occurring was 5.6 µg/ml (patient 8). Peak concentrations after standard daily doses of 450 or 600 mg in European patients range from 5–10 µg/ml (Verbist & Gyselen, 1968; Dans *et al.*, 1970; Furesz, 1970) and thus our patients developed symptoms at times when the rifampicin concentrations were usually well above those seen on daily treatment. However, patients 11 and 12, who had no symptoms, had similar concentrations of rifampicin to the patients with symptoms. Moreover, this explanation would not account for the observation that an initial daily phase of rifampicin or a small daily dose of rifampicin between the larger doses, reduces the incidence of symptoms (Girling, 1973; Hong Kong Tuberculosis Treatment Service, British Medical Research Council, 1973), nor would it account for the observation that the syndrome usually only starts after several weeks of intermittent treatment and is commoner when the same dose of rifampicin is given once a week rather than twice a week (Aquinas *et al.*, 1972).

It is of particular interest that out of the three patients who developed transient jaundice during an attack of the 'flu' syndrome (patients 5, 7 and 10), two (5 and 7) had unusually high rifampicin concentrations at 24 hr. This suggests that there may have been some interference, albeit only temporary, in hepatic or renal clearance of the drug. It is already known that bile and serum concentrations are increased in patients with hepatic impairment, particularly when associated with obstructive jaundice and the excretion half-life may be longer than in normal patients (Dettli & Spring, 1969). Moreover, acute renal failure may follow rifampicin administration (Poole *et al.* 1971; Hasse *et al.*, 1971; Kleinknecht, Homberg & Decroix, 1972; Seufert, 1973) and at least some of these cases have been suspected of having an immunological basis.

Although the present evidence is not conclusive it would seem likely that the 'flu' syndrome has an immunological basis and further evidence should be sought.

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References

- AQUINAS, M., ALLAN, W.G.L., HORSFALL, P.A.L., JENKINS, P.K., WONG, HUNG-YAN, GIRLING, D., TALL, R., FOX, W. (1972) Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *British Medical Journal*, **i**, 765.
- BATTEN, J. (1969) Rifampicin in treatment of experimental tuberculosis in mice. *Tubercle*, **50**, 294.
- BLAJCHMAN, M.A., LOWRY, R.C., PETTIT, J.E. & STRADLING, P. (1970) Rifampicin-induced immune thrombocytopenia. *British Medical Journal*, **iii**, 24.
- DANS, P.E., MCGEEHEE, R.F., WILCOX, C. & FINLAND, M. (1970) Rifampicin: antibacterial activity *in vitro* and absorption and excretion in normal young men. *American Journal of the Medical Sciences*, **259**, 120.
- DECROIX, G., KREIS, B., SORS, C., BIREMBAUM, J., LE LIRZIN, M. & CANETTI, G. (1969) Comparaison entre les régimes rifampicine—isoniazide administré quotidiennement et rifampicine—isoniazide administré deux fois par semaine. *Revue de la Tuberculose et de Pneumologie*, **33**, 751.
- DECROIX, G., KREIS, B., SORS, C., BIREMBAUM, J., LE LIRZIN, M. & CANNETTI, G. (1971) Etude comparative du traitement de la tuberculose pulmonaire par l'association rifampicine—isoniazide administrée quotidiennement et deux fois par semaine pendant une année. *Revue de la Tuberculose et de Pneumologie*, **35**, 39.
- DETTLI, L. & SPRING, P. (1968) Factors influencing drug elimination in man. II. *Farmaco*, **23**, 795.
- DICKINSON, J.M. & MITCHISON, D.A. (1970) Suitability of rifampicin for intermittent administration in the treatment of tuberculosis. *Tubercle*, **51**, 82.
- DUKOR, P., SCHUMANN, G. & DIETRICH, F.M. (1973) Immunological studies with rifampicin. Proceedings of the Workshop on Intermittent Rifampicin, Stockholm, October 2–3, 1972. *Scandinavian Journal of Respiratory Diseases* (in press).
- FARR, R.S. (1958) The febrile response upon injection of bovine albumin into previously sensitized rabbits. *Journal of Clinical Investigation*, **37**, 894.
- FARR, R.S. (1959) Fever as a manifestation of experimental allergy. *Journal of Allergy*, **30**, 268.
- FARR, R.S., CAMPBELL, D.H., CLARKE, S.L. & PROFFITT, J.E. (1954) The febrile response of sensitized rabbits to the intravenous injection of antigen. *Anatomical Record*, **118**, 385.
- FURESZ, S. (1970) Chemical and biological properties of rifampicin. *Antibiotica et Chemotherapia*, **16**, 316.
- GIRLING, D.J. (1973) Hong Kong Treatment Services/Hammersmith Hospital/British Medical Research Council co-operative study of rifampicin plus ethambutol in daily and intermittent regimens. Proceedings of the Workshop on Intermittent Rifampicin, Stockholm, October 2–3, 1972. *Scandinavian Journal of Respiratory Diseases* (in press).
- GRUMBACH, F., CANETTI, G. & LE LIRZIN, M. (1969) Rifampicin in daily and intermittent treatment of experimental murine tuberculosis, with emphasis on late results. *Tubercle*, **50**, 280.
- GYSELEN, A., VERBIST, L., COSEMANS, J., LACQUET, L.M., PRIGNOT, J., SIMON-POUTHIER, F., DEBRABANDERE, R. & DEVRIENDT, J. (1969) A co-operative study on rifampicin in original treatment of advanced pulmonary tuberculosis. *Acta Tuberculosea et Pneumologica Belgica*, **60**, 563.
- HASSE, W., POHLE, H.D., WARNECKE, F. & WIEK, K. (1971) Hamolytische krise durch rifampicin. *Praxis d'Pneumologie*, **25**, 466.
- HONG KONG TUBERCULOSIS TREATMENT SERVICES/BRITISH MEDICAL RESEARCH COUNCIL (1973) A controlled clinical trial of small daily doses of rifampicin in the prevention of adverse reactions to the drug in a once-weekly regimen of chemotherapy. *Clinical Allergy*, **4**, 1.
- KLEINKNECHT, D., HOMBERG, J.C. & DECROIX, G. (1972) Acute renal failure after rifampicin (Letter). *Lancet*, **i**, 1238.
- LAKSHMINARAYAN, S., SAHU, S.A. & HUDSON, L.D. (1973) Massive haemolysis caused by rifampicin. *British Medical Journal*, **ii**, 282.
- MITCHISON, D.A. (1973). *In preparation*.
- MOTT, P.D. & WOLFF, J.M. (1966) The association of fever and antibody response in rabbits immunized with human serum albumin. *Journal of Clinical Investigation*, **45**, 372.
- NEWMAN, R., DOSTER, B., MURRAY, F.J. & FEREBEE, S. (1971) Rifampicin in initial treatment of pulmonary tuberculosis. *American Review of Respiratory Diseases*, **103**, 461.

- PINES, A. (1971) Rifampicin with ethambutol for drug-resistant tuberculosis. *British Journal of Diseases of the Chest*, **65**, 178.
- POOLE, G., STRADLING, P. & WORLLEDGE, S. (1971) Potentially serious side effects of high-dose twice-weekly rifampicin. *British Medical Journal*, **iii**, 343.
- ROPARS, C., GERBAL, A., PONCEY, C., CARTRON, J., DOINEL, C. & SALMON, C. (1971) Accident transfusionnel de type anaphylactique en rapport avec un anticorps anti-IgA. *Revue Française de Transfusion*, **14**, 401.
- SCHMIDT, A.P., TASWELL, H.F. & GLEICH, G.J., (1969) Anaphylactic transfusion reactions associated with anti-IgA antibody. *New England Journal of Medicine*, **280**, 188.
- SEUFERT, C.D. (1973) Proceedings of the Workshop on Intermittent Rifampicin, Stockholm, October 2-3, 1972. *Scandinavian Journal of Respiratory Diseases*, (in press).
- SORS, C., SARRAZIN, A. & HOMBERG, J.C. (1972) Accidents hémolytiques récidivants d'origine immuno-allergique au cours d'un traitement intermittent par la rifampicine. *Revue de Tuberculose et de Pneumologie*, **36**, 405.
- VERBIST, L. & GYSELEN, A. (1968) Antituberculous activity of rifampicin *in vitro* and *in vivo* and the concentrations attained in human blood. *American Review of Respiratory Disease*, **98**, 923.
- WORLLEDGE, S. (1973) Correlation between the presence of rifampicin-dependent antibodies and the clinical data. Proceedings of the Workshop on Intermittent Rifampicin, Stockholm, October 2-3, 1972. *Scandinavian Journal of Respiratory Diseases* (in press).

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