Rh Immunization

SIR,—We are grateful to Dr. J. C. Woodrow for his comments (1 March, p. 572) and readily agree with his statement that mother-father ABO incompatibility does not inevitably result in mother-infant ABO incompatibility. The homozygous states AA and BB represent only 20% and 5% of the phenotypically A and B individuals, respectively. As Dr. Woodrow has stated, approximately 42% of the infants born to the incompatible A $\times$ O, B $\times$ O, A $\times$ B, B $\times$ A, and AB $\times$ A or B mating combination will be ABO compatible.

In the three studies we reviewed (15 February, p. 399) selection pressures were observed consistently for the group O women but not for the non-group O women. The area of disagreement between Dr. Woodrow and ourselves therefore revolves about the interpretation of the extent of risk for, or conversely protection against, maternal Rh immunization for group O Rh-negative women having Rh positive ABO incompatible infants.

The prospective Liverpool study, which includes observations of patients through subsequent Rh-positive pregnancies cited by Dr. Woodrow, is the only accurate means for estimating the true incidence of maternal Rh immunization when dual (ABO and Rh) incompatibility exists between mother and infant. In cases of dual incompatibility, the maternal anti-A and/or anti-B will reduce the mass of foetal antigen reaching the maternal spleen by sequestering the antigen in other organs. When the antigen mass is at the threshold level of immunization "sensibilization" or immunization without detectable antibody production becomes more common. In the study reported by Dr. J. C. Woodrow and Mr. W. T. A. Donohoe (19 October 1968, p. 139) and our study approximately 50% of the women immunized by ABO compatible Rh-positive pregnancies had no detectable anti-Rh until restimulated by a subsequent Rh-incompatible pregnancy. For the reason stated above one would anticipate the percentage of sensibilization would be even greater in ABO incompatibility.

The binomial confidence limits of the subsequent pregnancy data cited by Dr. Woodrow (3/86) are 0.6%–10%, which accommodates rather discordant interpretations. It appears that our original estimate (9–13%) of the risk of Rh immunization in group O Rh negative women having group A or B Rh positive infants is too high and we wait with anticipation further experience by the Liverpool group which will enable them to answer this question.—We are, etc.,

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Treatment of Angina Pectoris

SIR,—Many will agree with the view expressed by Dr. D. Verel (10 May, p. 380) that "more evidence is needed before it can be accepted that coronary dilators such as trinitrin and prenylamine lactate do not act by dilating coronary arteries."

With regard to prenylamine lactate, however, it should be remembered that there is also strong experimental evidence that this preparation does also have an effect on the myocardial metabolism as evidenced in particular by its effect on catecholamine uptake and storage.² It is our belief that these effects may well be more important than the direct coronary dilating effect. Therefore it is probably misleading to classify prenylamine as a coronary dilator. Certainly it is incorrect to consider it together with trinitrin or other nitrate derivatives; neither does it have a specific beta-adrenergic blocking effect.

As more work is done it becomes increasingly clear that we are still a long way from understanding the exact mode of action of the anti-angina preparations, and this is just as true for the new beta-blockers with their seductively simple-sounding rationale as it is for the classical trinitrin. On the other hand, as a practical means of everyday treatment prenylamine lactate 60 mg. has been shown to be safe and effective for long-term maintenance therapy of angina pectoris.^{3–7}—I am, etc.,

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Administration of Disodium Cromoglycate

SIR,—Dr. H. Herxheimer and Miss Helga Bewersdorff (26 April, p. 220) have expressed doubts on the method of administration of disodium cromoglycate with the Spinhaler on the basis of their microscopic examination of the powder content of the capsules. Their concern, which may be shared by others, is understandable, since we are dealing with both a novel appliance and a unique compound which probably acts topically at the site of the antigen reaginic antibody interaction.

The drug, as presented in the capsule, consists of micronized disodium cromoglycate in a size range providing more than 50% by weight between 2–6 μ (mass median diameter 2.6 μ , geometric standard deviation 1.4 μ , measured by the Coulter technique). The physical behaviour of such powders is dominated by surface forces (Van der Waal, electrostatic, adsorbed surface films, etc.) They are highly cohesive or "sticky" and become agglomerated into masses, with a lumpy appearance and poor flow properties. Since good flow properties are necessary for a powder to be dispensed from the Spinhaler the micronized disodium cromoglycate is mixed with lactose crystals in a size range of 30–60 μ to improve the inadequate flow of the micronized drug alone.

The Spinhaler has two distinct actions: (a) the transfer of the powder from the capsule into the air stream, and (b) the break-

up and dispersion of the powder cloud into fine particulate matter suitable for inhalation. Inhalation through the device causes the capsule to spin and vibrate, so that the powder is ejected into the passing air stream. High-speed photography reveals that the powder is metered through the pierced holes of the capsule in the form of agglomerates, the transfer being accomplished by a complex mechanical action.¹ The turbulent air streams inside the Spinhaler cause many agglomerates of drug and lactose to break up, and the resultant fine particles pass with the inhaled air into the respiratory tract. The remaining larger particles and agglomerates are, of course, retained in the upper airways. However, the locations in the lung where disodium cromoglycate is required to act have yet to be defined, so that the larger particles not necessarily capable of penetrating as far as the alveolar regions may in fact be necessary for therapeutic efficacy in some cases.

Urinary excretion studies in healthy volunteers have shown that about 9% of a 20-mg. dose inhaled from a Spinhaler is absorbed systemically in contrast to approximately 1% of an oral dose.² Thus about 8% of the total dose can be assumed to have been absorbed from the respiratory tract.

We agree with Dr. Herxheimer and Miss Bewersdorff that disodium cromoglycate can be administered satisfactorily by an aqueous nebulizer, always provided that an adequate dose can be deposited in the appropriate area of the lung. Because of the low solubility (approximately 10%) and high viscosity of the drug in water a power-operated nebulizer is necessary to deliver an adequate therapeutic dose. This method is therefore of limited use although it may be valuable for hospitalized patients.—We are, etc.,

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Research and Development Laboratories.
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Loughborough, Leics.

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Rejection of Suture Material

SIR,—It may be that a certain proportion of surgical wounds which break down and extrude stitches, with local reaction, are not in fact due to infection of the wound but to the patient's sensitivity to and intolerance of the suture material itself. Many surgeons have blamed themselves for the breakdown of wounds when the cause may have been outside their responsibility—and in the patient's own immune mechanism.

A doctor was seen recently who had undergone 12 surgical procedures. The first, an appendicectomy, was complicated by wound breakdown and the formation of a subphrenic abscess. Neither complication could be explained at the time. He next had a series of operations to remove the four menisci. The wounds of the first three of these operations all broke down between the fifth and 10th day with extrusion of stitches, sterile pus, and synovial sinus formation. London Hospital catgut had been used on each occa-

sion. The surgeon concerned diagnosed sensitivity to the suture material, and used linen thread on two subsequent operations to the knees, with uncomplicated healing. This procedure was followed without wound breakdown (except for a tonsillectomy where local reaction was severe) up to his eleventh operation. This was for evacuation of a large haematoma of the leg, which healed without complication. The patient was informed that catgut had been inserted, but in fact cautery only for the deep lesions had been used.

When a hand-tool severance of a radial artery had to be sutured urgently no mention was made by the patient of his suture intolerance, as he thought, after the haematoma, that it no longer existed. As suture materials the following were used: plain chromic catgut and monofilament nylon. Severe pain and swelling of the whole hand began the following day. Breakdown of the wound was now expected and it began on the seventh day, with nine stitches, eight catgut and one nylon, extruded over a period of four weeks. Pain, swelling, and inflammatory reaction with sterile pus discharge were present throughout.

The history of freedom from breakdown with linen and recurrence on return to catgut would seem to indicate a quite clear cause for wound breakdown. Suture intolerance may well be not uncommon.—I am, etc.,

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Vanderbijl Park,
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Repeat Prescriptions in Hospital

SIR,—With long-stay patients one of the problems is that their medication tends to be carried on more or less indefinitely and often unintentionally, or alternatively the same patient's medicine card may be presented for renewal and a different drug each day of the week. This is, of course, a shocking waste of nursing and medical time, and it also makes it extremely difficult for any doctor called to see a patient in an emergency to see exactly what drugs the patient is having.

NAME [REDACTED]

WARD Infirmary

No. [REDACTED] AGE 81

DATE	DRUG and DOSAGE	Time Prescribed for	Initials	Unit Supplied	Dates Supplied
16.3.69	Rx Chloral Hydrate 1.3 G. o.n.				16/3, 26/3
	Digoxin 0.25 } mgm.				28/3
	Neonaclex 2.5 } daily				28/3
	Slow-K 600 mgm. b.d.	2/12	PHG.		24/3
	Melleril 25 } mgm.				29/3
	Disipal 50 } i.d.s.				23/3
	inj. Cytamen 1000 µgm. alt. weds.				16/3
	inj. Proc. Penicillin 600,000 u. daily	(7)	PHG.		

In an attempt to solve this problem we have been using at this hospital a medicine card particularly designed for long-stay patients (see above). Drugs are written up for a specified length of time, and when this period has expired the medicines are reviewed en bloc. When a refill of the patient's medicine bottle is needed, the nurse has simply to fill in the date in the column on the right

"Cold" Cures and Monoamine-oxidase Inhibitors

SIR,—The recent article (15 February, p. 404) concerning the hazards from the use of monoamine-oxidase inhibitors and "cold remedies," brings up two other points—namely, that doctors and patients become careless, and also that the same substances at different times have different effects. I have known a physician who frequently washed down his phenelzine with whisky-and-soda, and also drank beer and wine. He had been doing this before any of the adverse hypertensive reactions were described and as he never had any "bad effects," he continued to do so.

A patient receiving nialamide 100-300 mg. per day had been warned about alcohol, but did not feel that this included her "two apricot sour" in the evening. Fortunately, she came to no harm. Some time ago I saw a 44-year-old manic depressive male who was receiving mebanazine 10 mg. t.i.d. from his private psychiatrist. For nearly five months he had accompanied this with a 10 mg. Dexedrine Spansule (sustained-release dexamphetamine sulphate) each morning. Despite being warned, he had continued to drink and was a large cheese eater and most catholic in his taste. While receiving the above medication he had eaten Muenster on several occasions, Port-Salut, Danish Blue, and Gorgonzola. However, one evening after two whiskies and a large portion of smoked cheddar cheese, on an empty stomach, he developed an excruciating headache and collapsed. He showed ptosis of the right eye and a minimal right facial nerve weakness. A spinal tap, carried out shortly after admission to the hospital revealed a pressure of 175 mm.

on the card and send it to the pharmacy. This system has the added advantage that bulk dose prescriptions can be sent to the pharmacy as soon as it opens and thus enable the pharmacist to carry on with routine tasks instead of wasting time waiting for the usual rush of medicine cards at midday.

This system ensures that all the medicines are reviewed regularly and makes it much easier to remember to carry out routine biochemical tests, particularly when patients are

having drugs such as diuretics, which may upset electrolyte balance, or haematinics, which may or may not be fulfilling their purpose adequately.

I am indebted to Dr. David Rice, medical superintendent of Hellingly Hospital, for permission to publish this letter.

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with a protein of 97 mg. A repeat tap three days later showed a pressure of 126 mm. and protein 68 mg. A diagnosis had not been made at this time. All other findings in the cerebrospinal fluid, blood, urine, electrocardiogram, etc., were within normal limits.

This case is of interest from several points of view, in that despite the knowledge of this type of reaction it was not considered at the time of admission to hospital, and indeed the writer made the diagnosis by telephone when consulted about the case; also this subject had repeatedly taken amphetamines, alcohol, and a variety of cheeses without any side-effects, but eventually he had a severe reaction. In addition to his transient neurological signs he showed a high C.S.F. pressure and protein. He made an uneventful recovery.

The only solution seems to be to warn against all drugs whatsoever, unless cleared; preferably to discuss this with a spouse or relative if available; to detail the knowledge about foods not to be eaten, and to interrogate the patient from time to time to make sure that instructions are understood and followed.—I am, etc.,

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Malarial Pigment

SIR,—In their account of splenomegaly in the tropics (11 January, p. 99) Drs. P. D. Marsden and P. J. S. Hamilton state that the length of time malaria pigment persists in the tissues of man is not known.

At the Ndola General Hospital percutaneous liver biopsies (Menghini needle) have been repeated in three patients in whose original biopsies malaria pigment was present in Kupffer cells, portal triads, or both. The interval between biopsies was 8, 40, and 41 months respectively. Each patient had had some form of antimalarial chemotherapy in the interim. In each case malaria pigment was not apparent in the repeat biopsy.

The first patient, with an interval between biopsies of eight months, was a 15-year-old male who had migrated from Rhodesia 11 years previously. After standard short courses of chloroquine and primaquine he was maintained on proguanil 100 mg. daily and continued to live in a malarious area. The second patient, interval between biopsies 40 months, was a young adult female who had moved from a malarious to a relatively malaria-free area shortly before the first liver biopsy. After biopsy a short course of chloroquine was administered and this patient continued to reside in a non-malarious area. The third patient was a 34-year-old policeman who received a short course of chloroquine and proguanil 100 mg. daily for two months after the first biopsy, and who continued to live in a relatively malaria-free area.

These patients formed part of an investigation into splenomegaly, and at the time of the first liver biopsy all had spleens palpable up to 6 cm. below the costal margin. At the time of repeat biopsy none showed palpable splenomegaly.

M. N. L. has permission from the Permanent Secretary for Health, Zambia, to publish this letter.

—We are, etc.,

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