the recent demonstration by J. M. Gupta and co-workers[8] that there is a considerable and often sustained rise in Po_2 after the injection of THAM into the umbilical vein. This effect must be due to a diminution of right-to-left shunting of blood, presumably the result of a direct effect of THAM or alkali in the lung, with lowering of the pulmonary vascular resistance. The administration of THAM via an umbilical artery instead of the vein had a much less beneficial effect.

This week in the *B.M.J.* Drs. J. M. Abraham and R. J. K. Brown report their results (page 640) of a clinical trial designed to compare intravenous (scalp vein) with intragastric administration of glucose and bicarbonate. Surprisingly, the infants who received their fluids by stomach tube had a somewhat lower mortality rate, though the difference was not statistically significant. It is, however, difficult to assess the possible harm of handling small, oedematous, premature infants in the manner which scalp vein infusions often entail. The use of the umbilical vein for intravenous fluid therapy carries some risk of phlebothrombosis in the portal vein, but this complication seems to be rare, and catheterization of either umbilical vein or artery involves a minimum of handling or exposure of the infant. Thus, while there is some evidence that correction of the metabolic acidosis by infusions of bicarbonate or THAM, and of fructose or glucose, under careful laboratory control does reduce the mortality rate, further studies are required to determine the precise effects of these substances and the best way of giving them.

The paramount importance of the accurately controlled administration of oxygen cannot be overstressed. Theoretically, hyperbaric oxygen should have advantages in the worst cases, but in both Glasgow[9] and Boston[10] it was found disappointing in practice. It cannot, of course, relieve CO_2 retention because of the great increase in functional dead space. Assisted respiration by intermittent positive[11] or negative[12] pressure is being tried in some centres for the treatment of deteriorating patients in whom the arterial Po_2 cannot be maintained at a safe level in 100% oxygen, or when the Pco_2 rises and stays above 70 mm. Hg, and especially when there are apnoeic attacks. It is not yet possible to assess the value of these very complicated and time-consuming techniques, which are by no means free of danger.

While there is room for controversy about the best methods of treatment of the respiratory distress syndrome, it is clear that the best results will be obtainable only in centres that can undertake throughout the twenty-four hours of the day the highly complex laboratory and therapeutic techniques required. They cannot be provided in every maternity unit, and these very ill babies should be transferred to a few special neonatal units which are staffed and equipped for this type of work. The portable incubator has made the transfer of the ill newborn baby a relatively simple matter, and each area should have an "infant flying squad" for this purpose.

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Single-dose Treatment of Pyelonephritis

In the study reported by Drs. R. N. Grüneberg and W. Brumfitt at page 649 of the *B.M.J.* this week the effect of a single dose of 2 g. of the very long-acting sulphonamide sulphormethoxine (Fanasil) was compared with that of ampicillin given in 500-mg. doses three times a day for seven days. Each treatment was successful in 22 out of 25 patients (88%). The two groups were comparable in age and sex, in frequency of a past history of urinary infection, which was obtained in a majority, and in that all had either an *Escherichia coli* or a *Proteus mirabilis* infection. Such good results could not be expected in infections due to other coliform bacilli (*Pseudomonas, Aerobacter,* and *Proteus* species other than *P. mirabilis*) or *Streptococcus faecalis* when treated with a sulphonamide. Side-effects were experienced by nine patients on ampicillin and by only two on sulphormethoxine, which was thus well tolerated, though, as the authors mention, larger doses have recently been found to produce skin reactions.

It is not claimed that sulphormethoxine gives better results than other sulphonamides. Another recent study[1] is mentioned in which a 90% cure rate was achieved with sulphadimidine. The advantages of sulphormethoxine are convenience, economy, and particularly the assurance that a full week of therapeutic effect will be secured, for patients instructed to take drugs daily sometimes omit to do so as soon as their symptoms are relieved. This is a leading advantage which has always been claimed for long-acting sulphonamides, though for most of them the claim has simply been that it is easier to remember one daily dose than three or four. There is the corresponding drawback that should any sensitivity reaction occur it is bound to be prolonged. This drug cannot, like another new sulphonamide, sulphasymazine, be eliminated more rapidly by alkalinizing the urine,[2] nor can it be surgically swabbed out of an injection depot, a treatment which might seem appropriate for such a severe and prolonged reaction to benzathine penicillin as that reported by H. C. Anderson.[3] Sulphormethoxine has not yet been used long enough to decide whether it shares the liability of other long-acting sulphonamides to produce the Stevens-Johnson syndrome, and Grüneberg and Brumfitt are probably wise in suggesting that it should not be administered to children until more experience with it has been gained.

Of the 50 patients treated 16 given ampicillin and nine given sulphormethoxine had a blood antibody titre against infecting organisms considered to be high enough to indicate renal involvement. This is a point of vital interest, because the effect of this sulphonamide must be exerted mainly in the tissues. Its half-life being about seven days, 1 g. of the dose given would be diluted in at least 10 litres of urine passed during that time, giving a concentration of at most 10 mg. per 100 ml., lower than that present in the blood. In ladies fond of their cups of tea (there is no mention of

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fluid restriction) the volume of urine passed in a week could have been considerably greater and the concentration of drug consequently lower. Even 10 mg. per 100 ml. seems inadequate for an antibacterial effect, particularly when acting on such large numbers of organisms as occur in infected urine. It therefore seems that these patients, in so far as their recovery was due to the treatment given (presumably some would have recovered spontaneously), owed it to the action of the drug in the tissues and not in the urinary tract. No such distinction need be made for ampicillin, which attains high concentrations in the urine as well as an adequate tissue level.

The question whether an action in the urine or in the tissues is more important has been argued for years. Clearly a tissue effect must be exerted when the substance of the kidney is affected. On the other hand, innumerable patients have incontestably been cured with mandelic acid or nitrofurantoin, neither of which attains an effective concentration except in the urine. The same is probably true of nalidixic acid. Is it to be concluded that in all these patients the kidney is not involved, and other tissues only superficially? The most difficult thing to explain is the similar proportion of successes claimed for drugs having different sites of action in unselected series of cases. Some act in both tissues and urine, several only in the urine, and here we have in sulphormethoxine one apparently incapable of exerting much effect except in the tissues. Yet it was successful in patients without as well as with evidence of renal disease. There is much in this subject which still remains to be explained, and it is not likely to be so except by the application of new and more searching methods to the study of patients undergoing treatment.

Chlorpromazine Melanosis

A side-effect of prolonged treatment with chlorpromazine is oculo-dermal melanosis.[1-3] In this condition the areas of skin exposed to sunlight become excessively pigmented and develop a violaceous or slaty-grey colour in the more severe cases. In the eye the lens, cornea, conjunctiva, and retina are affected.

The first changes usually occur in the lens. Brown or white granules are deposited under the anterior capsule in the pupillary area, and they may progress to form a disc- or star-shaped opacity. Granules also appear in the deeper layers of the cornea around Descemet's membrane; in some they appear also in the epithelium and anterior stroma. The early lens and corneal changes may be visible only with the slit lamp, but later they can be seen with an ophthalmoscope or the unaided eye. Pigmentation is also seen in the bulbar conjunctiva in the palpebral fissure. While no fundal changes were found in most of the surveys carried out[4-8] a few cases have been reported with clumping of pigment at the periphery of the retina or at the macula.[9-11] Some of these patients would have had more than one of the phenothiazine group of drugs, of which thioridazine in particular is a well-recognized cause of pigmentary choroido-retinopathy, but the rest of the patients had received only chlorpromazine.

These ocular changes have caused visual impairment in only a few cases.[5 9] In most of the surveys carried out no visual defects were found, though this may have been due to a lack of co-operation by the patients.[4-8] Electrodiagnostic tests of retinal function have generally been reported as normal,[5 11] but some cases with retinal changes had reduced potentials.[10] The pathological changes occurring in the skin[2] and conjunctiva[9] have been shown by biopsy to consist of clumps of pigment, with the staining characteristics of melanin, clustered round the blood vessels in the dermis. No other pigment has been found histologically, but reflection spectrophotometry[12] suggests that while in the mild cases the pigment was melanin in the more severe ones there was some other pigment present as well. Electronmicroscopical reports are conflicting. One author found[13] the typical appearance of melanin in the skin with some additional osmiophilic particles in the endothelial cells of the blood vessels of the dermis, while another author[14] found no "natural" melanin in the dermis. Lens changes have been produced in guinea-pigs by the administration of chlorpromazine and irradiation with ultra-violet light; extracts of these lenses together with the cornea showed a high concentration of the drug.[15]

So it would seem probable that both melanin and a drug metabolite are deposited in the skin and eye to cause the observed changes. In several post mortem examinations carried out on patients who died suddenly while on chlorpromazine therapy it was found that all the internal organs were heavily infiltrated with melanin,[16] and it has been suggested that infiltration of the heart may cause irregular rhythm, resulting in death. Tests of renal and hepatic function are often abnormal in patients on chlorpromazine therapy.

The condition has been described mainly among the inmates of mental hospitals because it occurs in patients who have taken large doses of chlorpromazine for long periods. The ocular changes seem to be clearly related to the amount of drug given and also to the daily dose.[17] While early reports suggested that affected patients had taken at least 500 g., later reports showed that melanosis could occur after smaller amounts.[6] Some investigators believe that the side-effects are not common if the daily dose is small, even if more than 500 g. are given.[7 18] The side-effects are almost certainly related to the concentration in the body of chlorpromazine,

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