able chance of showing a reduction of half or more in the stroke rate.[6] Between 1971 and 1976 the 24 participating centres across Canada enrolled 585 patients who had had at least one episode of transient cerebral or retinal ischaemia in the preceding three months. About one-third of the patients had residual neurological deficits beyond the conventional 24-hour period. Patients with events in both the carotid and vertebrobasilar distribution were included, but those subjected to surgery were not. A total of 144 patients received aspirin alone (325 mg four times daily); 156 received sulphinpyrazone alone (200 mg four times daily); 146 received both drugs in the above dosages; and 139 received placebo. With this design the 290 aspirin takers could be compared with the 295 no-aspirin takers, and the 302 sulphinpyrazone takers compared with the 283 no-sulphinpyrazone takers. Follow-up averaged 26 months and was complete in 99% of patients; the treatment compliance rate was 92%. The clinically "hard" events of stroke and death were analysed together by the log-rank life table method, which compares observed and expected numbers of events. Unfortunately some stroke events were not clearly defined and appeared identical with some episodes that qualified patients for entry into the trial. Only 57 patients were withdrawn because of side effects; no patients taking only aspirin developed haematemesis or melaena.

Sulphinpyrazone did not reduce the risk of stroke and death significantly, but aspirin did do so by 31%—just significant at the 5% level. Part of this effect seemed to be due to the sulphinpyrazone-only group faring rather badly, while patients taking both drugs fared relatively well. The results are difficult to interpret, since the patients taking only aspirin seem to have done very much as expected on the null hypothesis. The reduction of risk in men taking aspirin was 48% ($P < 0{\cdot}005$), but women had an increased risk which, though not significant, was contrary to the overall trend. Regrettably, an earlier trial was too small to show a significant effect of aspirin on the frequency of stroke, though transient episodes were reduced.[7]

The factorial design is very efficient for simultaneous testing of two treatments not expected to be synergistic (or to interact in the statistical sense). Nevertheless, the use of this design has complicated the interpretation of the Canadian results, since there may have been an interaction (albeit statistically insignificant) between aspirin and sulphinpyrazone: the 146 patients taking the combination treatment had the lowest risk of stroke and death. The lack of a significant difference between these patients and the 139 on placebo may have been because the numbers were too small. Clearly, another large trial should be mounted to examine the efficacy of aspirin alone in comparison with placebo. A daily or twice daily dosage would be easier for routine clinical management, though any further study should probably use a total daily dose similar to that in the Canadian trial. A smaller and less frequent dose may have profound antiplatelet effects,[8] but negative results would be difficult to interpret. Further trials need not be particularly expensive or complex, but they will require several hundred patients and ought therefore to be organised among several collaborating centres. One such trial is about to begin in Oxford, where the department of the regius professor of medicine hopes to recruit 6000 doctors into a three- to six-year trial to assess the prophylactic effects of aspirin on myocardial infarction in people with no history of heart disease.

The important conclusion to be drawn from the Canadian co-operative study is, contrary to the participants' prediction, that sulphinpyrazone does not prevent stroke and death when given alone. The results of this single trial do not provide enough evidence to recommend that men with transient cerebral or retinal ischaemia should be treated with aspirin. Preventing stroke still depends mostly on the adequate treatment of hypertension; but it is important that controlled trials of antiplatelet drugs—particularly aspirin—should continue.

[1] Ross Russell, R W, in *Cerebral Arterial Disease*, ed R W Ross Russell. Edinburgh, Churchill Livingstone, 1976.
[2] Veterans Administration, *Journal of the American Medical Association*, 1967, **202**, 1028.
[3] Veterans Administration, *Journal of the American Medical Association*, 1970, **213**, 1143.
[4] Fields, W S, *et al*, *Journal of the American Medical Association*, 1970, **211**, 1993.
[5] Brust, J C M, *Neurology*, 1977, **27**, 701.
[6] Canadian Co-operative Study Group, *New England Journal of Medicine*, 1978, **299**, 53.
[7] Fields, W S, *et al*, *Stroke*, 1977, **8**, 301.
[8] Burch, J W, *et al*, *Journal of Clinical Investigation*, 1978, **61**, 314.

Possible treatment for RDS

Surfactant deficiency was recognised as the cause of the respiratory distress syndrome (RDS) 20 years ago,[1] but treatment is still symptomatic: we still cannot replace the missing surfactant. Recent research into the properties of a synthetic surfactant holds out some promise for the future.

Natural surfactant is a mixture of lipids. The main component is dipalmitoyl phosphatidylcholine, whose behaviour, subtly modified by the other lipids, gives surfactant its vital physical properties. Surfactant forms a complete monolayer at the air-alveolar surface, covering the water lining the alveoli, producing a low surface tension, and so making expansion of the lung easier. During expiration the monolayer is compressed, changing its physical state from liquid to a more solid form,[2] and this stabilises the alveoli against atelectasis. The monolayer is continually being lost and replaced and can be maintained only by simultaneous secretion of sufficient surfactant. Immature or metabolically compromised lungs cannot synthesise or secrete enough surfactant and hence the surface tension rises and the surface pressures drop, so that more force is needed to expand the lungs. In weak or immature babies this cannot be overcome, and the result is atelectasis and clogging of the lungs with proteinaceous exudates.

An effective synthetic surfactant must, then, form an intact monolayer with a low surface tension over the whole surface of the lung; spread rapidly to cover the surface and keep the monolayer intact during respiratory movements; donate molecules quickly to the surface to replenish the losses; and form a "solid" layer during expiration to stabilise the alveoli.

Several workers have tried simply to replace surfactant with nebulised dipalmitoyl phosphatidylcholine.[3–5] This does not work, and is, furthermore, theoretically unsound. Pure dipalmitoyl phosphatidylcholine does not spread at temperatures below 41°C.[6] What is needed is a mixture of lipids which can lower the transition temperature of dipalmitoyl phosphatidylcholine and thereby aid its spreading.[7] Another problem is nebulisation.[8] Surfactant-in-water is slow at forming a monolayer because the phospholipids cannot rapidly escape to the surface as they are in the form of liposomes. In contrast, "dry" surfactant donates molecules rapidly and continuously

on to an aqueous surface. A suspension of particulate surfactant inserted into the trachea of premature rabbits aids lung expansion, gas retention, oxygenation, and survival time.[9-12] Studies on surfactant-depleted rats have shown that instilled or nebulised dipalmitoyl phosphatidylcholine, or nebulised natural surfactant, has little effect on lung residual capacity but that when a surfactant suspension is instilled there is a striking increase.[13]

This evidence suggests that a mist of phospholipid liposomes is unlikely to be useful in treating RDS but that relatively dry surfactant particles placed in the bronchi would spread to the alveoli and be effective. If synthetic surfactant is to work it must be given early—before atelectasis and hyaline membranes block the alveoli. A mixture of phospholipids in a dry form, a technique of administration, and the right dose may provide the basis for a specific treatment for the respiratory distress syndrome.

[1] Avery, M E, and Mead, J, *American Journal of Diseases of Children*, 1959, **97**, 517.
[2] Morley, C J, *et al*, *Proceedings of the Fifth Study Group of the Royal College of Obstetricians and Gynaecologists*, p 261. London, RCOG, 1977.
[3] Robillard, E, *et al*, *Canadian Medical Association Journal*, 1964, **60**, 54.
[4] Chu, J, *et al*, *Pediatrics*, 1967, **40**, 709.
[5] Shannon, D C, and Bunnell, J B, *Pediatric Research*, 1976, **10**, 467.
[6] Träuble, H, Eibl, H, and Sawada, H, *Naturwissenschafen*, 1974, **61**, 344.
[7] Ivey, H, Roth, S, and Kattwinkel, J, *Pediatric Research*, 1976, **10**, 462.
[8] Morley, C J, *et al*, *Nature*, 1978, **271**, 162.
[9] Enhörning, G, and Robertson, B, *Pediatrics*, 1972, **50**, 58.
[10] Enhörning, G, Grossman, G, and Robertson, B, *Biology of the Neonate*, 1973, **22**, 126.
[11] Enhörning, G, *et al*, *American Journal of Obstetrics and Gynecology*, 1975, **121**, 475.
[12] Wallin, A, Burgoyne, R, and Enhörning, G, *Biology of the Neonate*, 1977, **31**, 245.
[13] Ikegami, M, *et al*, *Pediatric Research*, 1977, **11**, 178.

Dichloroacetate

A new approach to the treatment of lactic acidosis has come from the use of dichloroacetate. This organic acid lowers blood glucose concentrations in diabetic[1 2] and starved normal animals[3] through activation of the enzyme pyruvate dehydrogenase by inhibition of pyruvate dehydrogenase kinase, the enzyme converting pyruvate dehydrogenase from its active to inactive form.[4 5] The resultant increase in oxidation of pyruvate in peripheral tissues reduces the supply of gluconeogenic substrates such as lactate, pyruvate, and alanine to the liver, thus diminishing resynthesis of glucose via the Cori and alanine cycles.[3]

Recently Stacpoole *et al*[6] gave dichloroacetate (3-4 g/day for six to seven days) to maturity-onset diabetics and found a 24% reduction in fasting blood glucose concentrations and even bigger falls in plasma lactate concentration (73%) and plasma alanine concentration (82%).

Since treating maturity-onset diabetes with biguanides increases the circulating concentrations of lactate and alanine[7] Standl *et al*[8] examined the effects of adding dichloroacetate (400 mg/day) to treatment with buformin. They found no differences in blood glucose, lactate, or ketone concentrations over a normal day. The discrepancy between these results and those of Stacpoole *et al*[6] must have been due to the different doses of dichloroacetate which were used. Standl *et al*[8] did find, however, that the effect of exercise in raising lactate concentrations was reduced during treatment with dichloroacetate.

Stacpoole *et al*[6] also observed an effect on circulating lipids: the fasting concentration of plasma cholesterol was reduced by 22% and of triglycerides by 61%. The mechanism by which dichloroacetate produces these effects is unknown, though the effect on triglycerides may be due to enhanced oxidation to ketone bodies. Concentrations of ketone bodies rise during dichloroacetate treatment in animals[9] and man[6]; this may be due either to enhanced oxidation of triglycerides or to increased production of acetyl CoA from pyruvate. Indeed, the action of dichloroacetate in raising circulating concentrations of ketone bodies (due to enhanced ketogenesis or decreased peripheral utilisation) provides grounds for reservation about its use in maturity-onset diabetics. Longer-term treatment will be needed to see if the effect persists. For the time being, treatment with a combination of biguanides and dichloroacetate must be considered of doubtful value, since maturity-onset diabetics treated by biguanides have raised blood ketone body concentrations,[7] which may be further raised by dichloroacetate.

Where the mechanism of action of dichloroacetate is likely to be valuable is in treating lactic acidosis. It is effective in preventing the hyperlactataemia associated with giving phenformin to animals[9] and in correcting their mild phenformin-induced lactic acidosis.[10] The mortality rate of biguanide-induced lactic acidosis in man is over half,[11] and this partly reflects how few successful treatment regimens there are. Alkalinisation has been the mainstay of treatment—aimed at raising the pH above the critical level below which the liver ceases to consume lactate and starts to produce it instead.[12] Other approaches to treatment such as the combination of insulin and glucose,[13] peritoneal dialysis, or haemodialysis[14] have their supporters; they may be necessary when hypoglycaemia is present or when alkalinisation in the presence of oliguria or anuria leads to sodium overload, but they have not been shown to reduce the mortality rate.

Few cases of lactic acidosis in diabetics have been treated by dichloroacetate,[15 16] and it is too early to assess the effectiveness of the regimen. Moreover, there has been some severe criticism of the published reports.[17] In severe phenformin-induced lactic acidosis in rats, however, dichloroacetate was not effective in reversing the acidosis when used alone.[10] Clearly it should not be used to the exclusion of other modes of treatment. Nevertheless, the exciting combination of hypoglycaemic, hypolactataemic, and hypolipidaemic effects in one compound merit further evaluation.

[1] Lorini, M, and Ciman, M, *Biochemical Pharmacology*, 1962, **11**, 823.
[2] Eichner, H L, Stacpoole, P W, and Forsham, P H, *Diabetes*, 1974, **23**, 179.
[3] Blackshear, P J, Holloway, P A H, and Alberti, K G M M, *Biochemical Journal*, 1974, **142**, 279.
[4] Whitehouse, S, and Randle, P J, *Biochemical Journal*, 1973, **134**, 651.
[5] Whitehouse, S, Cooper, R H, and Randle, P J, *Biochemical Journal*, 1974, **141**, 761.
[6] Stacpoole, P W, Moore, G W, and Kornhauser, D M, *New England Journal of Medicine*, 1978, **298**, 526.
[7] Nattrass, M, *et al*, *Diabetologia*, 1977, **13**, 145.
[8] Standl, E, Janka, H-U, and Standl, A, *Diabetologia*, 1977, **13**, 433.
[9] Holloway, P A H, and Alberti, K G M M, *Diabetologia*, 1975, **11**, 350.
[10] Holloway, P A H, and Alberti, K G M M, *Diabetologia*, 1977, **13**, 402.
[11] Luft, D, Schmülling, R M, and Eggstein, M, *Diabetologia*, 1978, **14**, 75.
[12] Lloyd, M H, *et al*, *Clinical Science and Molecular Medicine*, 1973, **45**, 543.
[13] Dembo, A J, Marliss, E B, and Halperin, M L, *Diabetes*, 1975, **24**, 28.
[14] Hayat, J C, *Diabetologia*, 1974, **10**, 485.
[15] Irsigler, K, Kaspar, L, and Kritz, H, *Lancet*, 1977, **2**, 1026.
[16] Irsigler, K, *et al*, Presentation to German Diabetes Federation, Dusseldorf, 1978.
[17] Alberti, K G M M, Nattrass, M, and Holloway, P A H, *Lancet*, 1977, **2**, 1136.