

era? These factors have not figured prominently in analyses of vaccine associated paralysis, and the familiar routine administration of both oral attenuated poliovaccine and triple diphtheria, tetanus, and pertussis vaccine to children has not proved dangerous. In particular, the pertussis vaccine has not emerged as an agent provocateur for poliomyelitis associated with oral attenuated poliovaccine.

Any case of acute paralysis which might possibly be due to poliovirus, whether after vaccination or otherwise, should be immediately investigated by testing stool specimens for the presence of virus. Virulent polioviruses still abound in the world and may be imported into countries such as Britain to exploit any gaps in individual or herd immunity. Occasional cases of paralytic poliomyelitis still occur in Britain in unvaccinated children and adults with or without recent travel abroad, and we must be on guard against any complacent, premature belief that this infection need no longer be considered in differential diagnosis.

Virological tests can distinguish vaccine derived from "wild" strains of poliovirus more accurately nowadays, and they can also identify the occasional cases of poliomyelitis due to those other enteroviruses against which poliomyelitis vaccines cannot be expected to protect. Continuing surveillance by both virological and epidemiological techniques is essential for satisfactory and sustained control. Meanwhile, better vaccines are on the way, though the present vaccines are so good that any improvements will be impossibly difficult to show in field trials.

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## Prostacyclin—powerful, yes: but is it useful?

To realise why we cannot answer the question asked in the title we need to take the story of the discovery of prostacyclin back to its unlikely origins in the work of two gynaecologists in 1930.<sup>1</sup> We must follow the trail through a period of quiescence and neglect until we reach an unprecedented explosion of research in the 1970s, culminating in the award of the 1982 Nobel prizes for medicine and the marketing of prostacyclin in 1983 (by then, and over 2000 scientific papers too late, renamed epoprostenol).

In 1930 the instillation of fresh human semen into the uterus was found to cause powerful muscular contraction or relaxation.<sup>1</sup> The activity resided in a lipid soluble acidic fraction, which could be further subdivided by ether and phosphate buffer extraction. Because the source of the active agents was thought to be the prostate they were named "prostaglandins," and because of the way in which ether and phosphate

are spelt in Swedish the subfractions were labelled prostaglandin E and prostaglandin F respectively. They were regarded as a curiosity or an irrelevance, though the structural studies carried out by Bergström and his colleagues<sup>2,3</sup> began to show that the biological activities were due to a family of unsaturated hydroxy acids with an entirely novel shape which resembled a hairpin bent around a five membered ring.

The existence of a large family of prostaglandins provided the explanation of the confusing and conflicting pharmacological results which hitherto had been obtained by testing body fluids and tissue extracts, and in the 1960s increasingly refined synthetic techniques made it possible to study individual prostaglandins instead of indeterminate mixtures of variable and shifting composition.

Individual pure prostaglandins were soon shown to have profound effects on tissues other than smooth muscle. The first link with the thrombotic story came in 1967, when prostaglandin E<sub>1</sub> was shown to be the most powerful inhibitor of platelet aggregation so far discovered<sup>4,5</sup> and to be capable of stopping injured animal arteries from forming platelet thrombi when it was infused intravenously.<sup>5</sup> Attempts to infuse it into man confirmed that platelet inhibition could be produced—but at a price in respect of vasoactive and gut side effects,<sup>6</sup> which we shall meet again as our story unfolds.

By now, the recognition of the universal distribution of prostaglandins and their powerful biological effects was blowing away the fog of neglect which had hidden them from general view for four decades. Soon they were found to play a crucial part in many disturbances of body function such as inflammation. Vane<sup>7</sup> showed that the therapeutic effects of salicylates and aspirin like drugs were due to their ability to prevent the synthesis of proinflammatory prostaglandins. This aspirin effect was due to inhibition of the cyclo-oxygenase enzymic step which transforms membrane arachidonic acid into the cyclic endoperoxides prostaglandin G<sub>2</sub> and prostaglandin H<sub>2</sub>. The hunt was then on for the identity of derivatives of these endoperoxides which were mediating the inflammatory response. Samuelsson and his colleagues<sup>8</sup> provided the answer when they showed that platelets and white cells could use the cyclic endoperoxides to generate a highly active substance which they named thromboxane. This was found to have a short half life; the initial, short lived compound was named thromboxane A<sub>2</sub> and its stable derivative thromboxane B<sub>2</sub>. Thromboxane A<sub>2</sub> was found to have intense vasoconstrictor, bronchoconstrictor, and cytolytic activity as well as being a very powerful platelet aggregator.

The final step in the chain that led to the marketing of prostacyclin (alias epoprostenol) came in 1976 when the Wellcome group<sup>9</sup> found that vessel walls could use the same arachidonate derived endoperoxides, prostaglandin G<sub>2</sub> and prostaglandin H<sub>2</sub>, to generate an unstable material which had diametrically opposing properties to thromboxane A<sub>2</sub>; this artery derived substance (which they named prostaglandin X but was subsequently rechristened prostaglandin I<sub>2</sub> and prostacyclin) was a vasodilator, a bronchodilator, a cytoprotective, and a very powerful inhibitor of platelet aggregation. Indeed the concentration of prostaglandin E<sub>1</sub>, previously regarded as the most powerful natural inhibitor of aggregation, which inhibited adenosine diphosphate aggregation by half was 21 ng/l while for prostacyclin it was only 0.4 ng/l.<sup>10</sup>

The complementary nature of thromboxane A<sub>2</sub> and prostacyclin led to increasing speculation about their Yin and Yang functions in the economy of the body in health and disease. Might the blood be maintained in its normal fluid state only because "good" prostacyclin from vessel walls kept "bad"

thromboxane  $A_2$  from platelets at bay?<sup>11</sup> Might the functioning of distant body tissues and cells be controlled by prostacyclin released from the lungs which was acting as a hormone by resetting cellular cyclic adenosine monophosphate and calcium concentrations?<sup>12</sup> The history of these ideas and their present state is fully documented in the July 1983 *British Medical Bulletin*, which is entirely devoted to prostacyclin, thromboxane, and leukotrienes.

So much for the background; now for the task in hand, which is to appraise the prospects of prostacyclin as a therapeutic agent, since a formulation for intravenous use ("Flolan") has just been launched. The suggestion is that the drug should be used to "keep platelets in circulation" in circumstances in which "artificial surfaces . . . cause activation, aggregation and consumption of platelets." This where a knowledge of history proves useful, since we can now say "But surely prostacyclin is a very unstable substance and will have powerful actions on tissues other than the platelets? Moreover, is it acting as a pharmacological agent because of its power in inhibiting platelets rather than as a physiological corrective?"

Early doubts had already been expressed<sup>13</sup>: "Imagine a drug with the following characteristics. It is inactive orally so has to be given intravenously. . . . Continuous infusion is required because the drug is rapidly eliminated with a half life of minutes. Most of the recipients complain of headache and all are flushed in the face. . . . Sudden bradycardia, nausea and pallor can occur without warning. Side effects are severe because the drug is usually given at the highest dose the patient will tolerate." The *Lancet's* anonymous leader writer regarded it as a marketing man's nightmare but wisely observed "it is hoped that prostacyclin will do well at stud, siring second generation agents which are better tolerated and easier to use and which have wider applications in vascular disease."

Lewis and Dollery have provided an excellent and timely review<sup>14</sup> of the actual therapeutic achievements of prostacyclin so far, and their comments can conveniently be divided into two sharply contrasting areas. The first is the ability of prostacyclin to minimise loss of platelets when blood is exposed to artificial surfaces such as in haemodialysis, cardiopulmonary bypass, and charcoal column perfusion for liver failure. In all of these techniques platelets may be deposited in the extracorporeal circuits, producing thrombocytopenia and bleeding in the patient; or they may be returned to the circulation as aggregates which may then embolise producing organ failure and microangiopathy. After reviewing all the available studies Lewis and Dollery accept that prostacyclin may be used as the sole antithrombotic agent in such systems but they add that "the doses of prostacyclin required as sole anticoagulant in extracorporeal devices are sufficiently large to cause marked side-effects in conscious patients. In such patients prostacyclin is most likely to be used as a heparin-sparing agent rather than as a complete replacement for it." They also point out that most patients can be adequately treated with these circuits without the use of prostacyclin and that the platelet sparing effects of the drug confer an appreciable but only marginal benefit. They believe that a stronger case can be made for the use of prostacyclin in charcoal perfusion than in the other systems because "the treatment cannot in some cases be carried out without the use of prostacyclin."

In respect of extracorporeal artificial surfaces the feasibility and immediate value of using prostacyclin has thus been well documented, and we now need to marshal evidence to determine whether overall mortality and morbidity will be improved by using it more widely. When the artificial surface is intracorporeal rather than extracorporeal a similar platelet sparing

effect can be shown.<sup>15</sup> The rate of deposition of platelets labelled with <sup>111</sup>In was noticeably reduced on prosthetic arterial grafts during infusion of prostacyclin and returned to its initial high value when the infusion was stopped. Outcome studies of graft patency and patient survival must now be mounted, for it may be that some blood cell deposition is necessary to form a natural protective lining on the prosthetic surface.

It is when Lewis and Dollery begin to consider the value of prostacyclin in conditions where no man made artificial surface activates the blood that they start to answer my title question—with a "Don't know."<sup>14</sup> In both thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, damaged vessel walls and intravascular fibrin strands have been thought to provide a disease made activating surface which cannot produce its own prostacyclin. In these circumstances prostacyclin would have been expected to spare platelets by preventing their consumption—and yet there is no convincing evidence that this occurs. The picture is even more confusing in disease of the limb arteries, whether of the atherothrombotic type leading to claudication, rest pain, gangrene, and amputation or the "vasospastic" type with Raynaud's phenomena. The original uncontrolled observations<sup>16</sup> on the effect of intra-arterial prostacyclin claimed that it produced an improvement in the healing rate of gangrenous ischaemic limbs which was maintained for several months, even though the infusions had spanned only a period of days. The clinical course of peripheral vascular disease is so variable that many candidate drugs and their proponents have fallen prey to the trip wires and the anti-personnel mines which defend the area. More recent studies have given conflicting results, but there is still a hint of benefit which outlasts the known pharmacological properties of the drug. Lewis and Dollery conclude that "at present it is not possible to draw any definite conclusions about the value of prostacyclin in peripheral vascular diseases. More double-blind studies are needed. It is difficult to see how a drug that is only a weak vasodilator and that causes a short-lived but marked effect upon platelets could have a longlasting therapeutic action." The latter point may not be insurmountable, for in our early studies<sup>6</sup> of infusions of prostaglandin  $E_1$  we found that the observed effects outlasted the circulatory life of the infused material. If prostacyclin similarly changes some fundamental property such as cellular cyclic adenosine monophosphate or calcium flux then it will be the half life of this change rather than of the prostacyclin itself which will determine the duration of the effect.

Lewis and Dollery also review some studies of prostacyclin in a wide range of other conditions (angina, pulmonary hypertension, asthma, pregnancy induced hypertension, renal graft rejection, and cardiac failure). Understandably, they can offer no helpful conclusions and like me<sup>17</sup> they must be sad at the tremendous imbalance between the worldwide interest in the discovery of prostacyclin and the lamentable lack of adequate clinical trials of its efficacy. Since their review, further completely uncontrolled observations have been published claiming that prostacyclin may be of benefit in stroke,<sup>18</sup> and in my view "unless we are prepared to put as much effort into testing for clinical effectiveness as we put into basic research and development our patients might be better off if we stopped searching for antithrombotic drugs and concentrated instead on simple manoeuvres of current proved value such as cessation of smoking and better blood pressure control."<sup>17</sup>

And yet it is hard to see how major studies can ever be mounted in common and lethal or disabling vascular diseases such as venous thromboembolism, myocardial infarction, stroke, and limb gangrene using prostacyclin itself because of

its instability, its short duration of action, and its requirement for carefully monitored infusion techniques.

For the present, then, we must accept that prostacyclin is indeed powerful and useful in extracorporeal shunts. How ironic that, despite its early claims to be a natural balancing substance in the thrombotic equation, the usefulness of prostacyclin has been most clearly proved in entirely man made settings where blood meets an artificial surface. In the common spontaneous vascular diseases we must recognise that not only is prostacyclin not yet of proved value but that it is unlikely to be so. The real hope here lies in the exploitation of this novel compound to generate a stable, orally active prostacyclin analogue which will have selective affinity for the platelet receptors and will have minimal effects on the heart and blood vessels. Like the inventor who answered his critics by saying "But what is the use of a newborn baby?" we should be prepared to say of epoprostenol "Wait till it grows up and has children of its own—for what the world is waiting for is 'Son of Prostacyclin.'"

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## Legislation and teenage sex

To paraphrase Jane Austen, it is a truth universally acknowledged that parliament should not make new laws when those most closely affected advise that the proposed legislation is unwise and unworkable. Earlier this month the BMA called a press conference to leave the press and public in no doubt that doctors do not want any change in the law governing the prescription of oral contraceptives for girls under the age of 16. No one doubts the good intentions of most of those who want to prohibit doctors from prescribing the pill in these circumstances without the consent of the girl's parents; but the campaigners have mostly been arguing from conviction rather than experience. The attitude of doctors would have been very different if the call for legislation had come from the families directly affected—namely, those in which 14 and 15 year olds have been prescribed the pill—or from doctors working with teenagers. In practice the pressure has mostly come from adults shocked by reports of promiscuous sexual behaviour among adolescents but with little or no direct experience of the realities.

Doctors in family planning clinics or in general practice who are asked for advice on contraception by teenage girls have to make a pragmatic assessment. Almost always these girls have already formed a sexual relationship, often stable and overt. Most have no wish to keep their mothers in the dark; of those few who do ask for confidentiality, one third can be persuaded at the first interview to tell their parents and another third agree later.<sup>1</sup> The remaining third of girls must believe they have very strong reasons for rejecting the doctor's advice—for doctors do always make an attempt to bring the parent into the picture.<sup>2</sup> Who will gain from a law insisting that in these circumstances the girl should be told that she may not be supplied with a contraceptive?

At the heart of the matter are the very different ways in which people think of teenage sexuality. Should pregnancy be seen as a punishment for illicit sex? Is fear of pregnancy really an important deterrent? If sexually active teenagers are denied access to medical contraception are they more likely to stop having sex or to use some unreliable contraceptive technique that requires no prescription?

The BMA press conference spelt out the medical hazards of early sexual experience and of pregnancy; doctors working with schoolchildren are only too aware of the physical and psychological problems that may sometimes be associated with sexual activity in the early teens. But like it or not, doctors have to work in the real world. Over the years we have worked out a whole range of compromise solutions that seem to minimise damage to our patients; intending legislators should be extraordinarily certain that they have found a better answer.

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