Looking back

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Phototherapy

R. H. DOBBS and R. J. CREMER

The story of how a little light came to be shed on jaundiced newborns is told by Dr. R. H. Dobbs, a former Editor of the *Archives*, at present Professor of Child Health at Ahmadu Bello University, Zaria, Nigeria, and Dr. R. J. Cremer, now a general practitioner in Wallington, Surrey.

The initial observations

R. H. DOBBS

In the early 1950s interest in rearing premature infants centred firstly around growing knowledge concerning the respiratory distress syndrome; secondly the emergence, with the increasing effectiveness of incubators, of retrolental filroplasia; and thirdly the development of replacement transfusion to combat not only the excessive bilirubinaemia resulting from blood incompatibility, but also the much more gradual rise seen in premature infants.

The premature unit at Rochford General Hospital, Essex, had been developed out of a group of rooms designed, in the days before the war, as a puerperal sepsis unit disposed around a paved courtyard open to the south and, when it shone, to the sun. The arrival of sulphonamides in the years immediately before the war and of penicillin during the war, having rendered a puerperal sepsis unit redundant, it was by a mixture of luck, sharp practice, and lack of competing opposition, seized upon as an ideal, almost purpose-built premature baby unit.

Sister J. Ward (Fig.), the sister in-charge of the Premature Unit (chosen because of her known skill in rearing puppies) was a keen fresh air outdoor fan, and on warm summer days would wheel the more delicate infants out into the courtyard, sincerely convinced that the combination of fresh air and warm sunshine would do them much more good than the stuffy overheated atmosphere of an incubator. Sister Ward well knew of the anxiety engendered by this practice and hastily brought the infants safely

FIG.—*Miss J. Ward. S.R.N., in 1956, with one of the earliest of the infants given phototherapy at Rochford General Hospital.*

in when consultant rounds were imminent; and, as no harm seemed to be done, the practice was tacitly allowed to continue.

One particularly fine summer's day in 1956, during a ward round, Sister Ward diffidently showed us a premature baby, carefully undressed and with fully exposed abdomen. The infant was pale yellow except for a strongly demarcated triangle of skin very much yellower than the rest of the body. I asked her, 'Sister, what did you paint it with—iodine or flavine, and why?' But she replied that she thought it must have been the sun. 'What do you mean Sister? Sun tan takes days to develop after the erythema has faded.' Sister Ward looked increasingly uncomfortable, and explained that she though it was a jaundiced baby, much darker where a corner of the sheet had covered the area. 'It's the rest of the body that seems to have faded.' We left it at that, and as the infant did well and went home, fresh air treatment of prematurity continued.

A few weeks later and still during the warm summer months, blood from another deeply jaundiced infant was sent to the laboratory. After an unusual delay of some hours, and increasing anxiety, the plasma bilirubin was reported over the telephone to be 13–14 mg/100 ml. This was so clearly wrong that a fresh specimen was taken directly up to the laboratory, and an explanation requested both for the delay and for what seemed to be a very much lower level of bilirubin than expected in so jaundiced a baby. Mr. P. W. Perryman, the Biochemist, said he was sorry about the delay: 'It should have been done before lunch: but I found the tube lying on the window sill and I did it myself, so I am sure it's correct'. And he undertook to repeat the estimation on what was left of the morning specimen which was still lying, in full sunlight, on the window sill. When he had finished, he said the new specimen had gone up to 24 mg/100 ml, but that he couldn't understand how it was that the old specimen seemed to be lower than ever and now read only 9 instead of 14 mg/100 ml as reported in the morning; at last light dawned.

These two 'happenings' stimulated us to look more carefully into the action of sunlight on bilirubin, and we were able quite soon to establish firstly, that bilirubin was indeed in some way affected by direct exposure but that it was not ultraviolet but visible blue light that was most effective; secondly, that it was only unconjugated bilirubin that was affected; and thirdly, that, as a therapeutic measure, light treatment was quite unable to cope with the torrent of bilirubin produced in cases of rhesus incompability, but did often seem able to hold the rise of bilirubin that occurs in premature infants and makes it possible to avoid a replacement transfusion.

Subsequent observations

R. J. CREMER

This adventure, which provided at different times excitement, frustration, and disappointment, began at Rochford General Hospital, Essex, some 20 years ago during the sunny summer months of 1956, and ended, at least for us, with the publication of our findings two years later (Cremer, Perryman, and Richards, 1958).

At the time, as paediatric registrar to Dr. R. H. Dobbs who was then Consultant Paediatrician, I was responsible for the day-to-day care of the occupants of the Premature Baby Unit, and for all exchange transfusions. Although the indications laid down by P. L. Mollison for exchange transfusion in rhesus cases (Coombs's test, haemoglobin and serum bilirubin levels on a cord blood sample) were widely accepted and generally acted upon, these seemed somewhat arbitrary and failed to take into account what would be happening in the infant during the next few hours and days. Accordingly it was agreed by Dr. Dobbs, that whenever possible, exchange transfusion should be delayed and blood samples taken from the infant at frequent intervals in order to discover the *rate* of rise of the serum bilirubin during the next few hours after birth. By employing this 'wait-and-see' tactic and recording the findings as a graph, the first few points provided a line indicating the rate of rise during this time and an early warning of whether the danger level was likely to be reached, and if so, when. It soon became apparent that some infants who hitherto would have qualified for exchange transfusion on their cord blood findings, did not require this as their serum bilirubin levels peaked below the generally accepted danger level and then fell. The most that was needed in such cases was a simple 'top up' transfusion if the degree of anaemia warranted it.

Despite what seemed a logical and safe diversion from the usual practice, such was the influence of the leading authorities on the subject that some of our colleagues regarded our activities with ill-disguised disapproval. However, thanks to the backing of Dr. Dobbs this became our policy and because of it many infants were spared unnecessary exchange transfusion.

As frequent blood samples were now to be taken from all babies with neonatal jaundice it was desirable that bilirubin estimations should be made

on less serum than was needed for the then conventional method. Our biochemist colleagues, P. W. Perryman and D. H. Richards, devised a micromethod based on the original procedure of King and Coxon but requiring only 0·1 ml serum which could easily be obtained by heel stab, so that venepuncture was no longer necessary (Perryman, Richards, and Holbrook, 1957).

It was during the course of an exchange transfusion one sunny July afternoon that an oversight led to an interesting observation. As usual a sample of blood was taken immediately before starting replacement and a second on completing the operation, in order to determine the resultant drop in serum bilirubin. On this occasion the pre-transfusion sample was mislaid; in fact it stood on a window sill in bright sunlight thoughout the time the transfusion was being carried out. When eventually found, it was noticed that *the serum was green instead of yellow* and the bilirubin content was far below what was expected. The test was repeated with fresh reagents but the result was the same. The ever reliable Sister Ward in charge of the Premature Baby Unit was questioned to make quite sure it was the right sample. There was no escaping the fact that while exposed to sunlight there had been a reduction in the bilirubin content of the sample. The green pigment was identified as biliverdin and as this, unlike bilirubin, was thought to be harmless to brain cells and probably more easily excreted, our interest was aroused still further. It seemed that we had stumbled on something that might have a practical application. Even at this stage we were able to learn something from our observation, for in future all blood samples for bilirubin estimation were placed in light-proof containers before being taken from the ward to the laboratory (Cremer *et al.*, 1957).

As luck would have it the sun continued to shine and from that day on blood samples were to be seen on the biochemistry laboratory window sill in the sunlight, behaving like traffic lights as they turned from red to yellow and then green. Samples of icteric serum in glass tubes were exposed to sunlight at controlled temperature and graphs plotted of the reduction in their bilirubin content. It was a constant finding that the bilirubin fell dramatically, showing conclusively that this was a light and not a heat effect.

Confirmation of a photo-oxidative action was given by a simultaneous increase in oxidation-reduction potential measured electrically. Using a paper-chromatographic separation of bilirubin-biliverdin it was found that even when run in nitrogen, a rapid oxidation of bilirubin occurred in daylight which was absent when run in the dark. Further experiments showed the unconjugated bilirubin predominating in icteric neonates to be two or three times as photosensitive as the conjugated form.

In the Premature Baby Unit, jaundiced infants were cautiously exposed to sunlight for short periods and their serum bilirubin levels estimated and plotted. Sister Ward, as intrigued as the rest of us, soon noticed that except where they were covered or a shadow was cast upon them the babies quickly lost their jaundice only to regain it when clothed. Not only did the babies lose their jaundice from the parts of their skin exposed to sunlight but their serum bilirubin levels fell quite impressively during this time. When removed from sunlight, jaundice returned and serum bilirubin levels rose but again fell when they were once more exposed to the sun.

Though greatly encouraged by this finding, rejoicing was short lived, as at this stage the sun deserted us. However, like good Englishmen, the laboratory contingent had anticipated this happening and already worked out the particular wavelength within the sun's spectrum responsible for the observed photodestruction of bilirubin. They found that when icteric serum of infants is illuminated by white light at a constant temperature of 20°C the characteristic 420 μm absorption peak decreases and absorption at the red end of the spectrum around 550–650 μm increases. At the same time the serum bilirubin level is reduced and electromotive force measurements show a positive increase in the oxidation/reduction potential of the system. This seemed to indicate that under the action of light, bilirubin undergoes photo-oxidation or dehydrogenation to biliverdin or some intermediate products, these substances being more polar and therefore probably more easily excretable than bilirubin.

So encouraging were the results obtained with natural sunlight that we were now eager to find an artificial light source of suitable wavelength that might safely be used to achieve the same results. At this stage the biochemistry laboratory began to look more and more like a store for every kind of electric light equipment—including a Southend street lamp—as each was examined to discover the wavelength it emitted. By trial and error we found that a simple 'blue fluorescent' tube was the best available source giving light of high intensity in the region of 420–48 μm, and settled for this with which to illuminate samples of icteric serum to see whether we could reproduce the earlier results obtained with sunlight.

Although somewhat less effective than sunlight, it

proved able to produce promising results and was perhaps safer. Delighted at the prospect of becoming independent of the wayward English climate, we embarked upon a series of tests to discover whether our new-found light source would be safe to shine upon babies, possibly for quite long periods.

To our great relief we found that only negligible amounts of ultraviolet and infrared, and no 'x' irradiation was emitted by our chosen light source, while the heat generated was thought likely to be more of an advantage than otherwise, as the babies would need to be kept warm during periods of illumination when they would be naked. However, it was one thing to illuminate samples of icteric serum in test tubes but obviously a very different matter if we were to shed the same light on jaundiced babies. Some form of suitable apparatus that would be electrically safe and not interfere with nursing care would be necessary. In no time the hospital engineers created what proved to be a very practical, adjustable light cradle incorporating eight 40-watt blue fluorescent tubes backed by a curved stainless steel reflector that could be placed above a standard infant cot. Special care was taken to ensure the electrical safety of the apparatus and a series of further tests were carried out to check for infrared, ultraviolet, and 'x' irradiation; the temperature in an empty cot was also recorded with the cradle at different heights above it.

At last it seemed we could safely proceed with illumination of jaundiced babies using our new apparatus, but frustratingly not a single case of neonatal jaundice occurred for what seemed like weeks. Eventually our chances did come and fortunately everything went according to plan. Care was taken to protect the baby's eyes by a simple plastic shield; particular vigilance was needed with this as head movements tended to displace it, and the infant's body temperature could be satisfactorily controlled by varying the height of the light cradle above the cot. In all other respects, nursing and feeding were carried out in the usual way, and no complications were encountered.

For reasons not fully understood, better results were obtained by intermittent illumination—6 hours on followed by 2 hours off, than by continuous exposure for longer periods.

In due course it became obvious that illumination was no substitute for replacement transfusion in the erythroblastotic infant with very active haemolysis, but was particularly valuable in the treatment of jaundice of prematurity, and that it could also obviate the need for replacement or repeat replacement in some of the milder cases of rhesus incompatibility. By combining the policy of making serial bilirubin estimations with illumination, the number of babies with hyperbilirubinaemia requiring exchange transfusion was demonstrably reduced.

As we had been sailing in uncharted waters, particular emphasis was placed on safety at all stages and at no time was exchange transfusion delayed when the need for it was clear.

Because of the simplicity, proven effectiveness, and above all what we believed to be the safety of the treatment, we submitted our findings to the *Lancet* and they were published in 1958. Ten years were then to pass before phototherapy was virtually rediscovered in America, and then quickly it gained a measure of recognition and respectability previously denied it in this country, with a few notable exceptions such as Dr. C. B. M. Warren at Chelmsford (Broughton *et al.*, 1965) and Dr. Herbert Barrie at Charing Cross Hospital (Barrie, 1970), who from the outset were enthusiastic advocates of its use. The final word should be one of recognizing the major contribution made by our biochemist colleagues, P. W. Perryman and D. H. Richards, for without their knowledge, ingenuity, and willingness to turn out at all hours, the project would never have begun, let alone been completed.

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