TRIAMCINOLONE

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'Is there anything of which it may be said, See, this is new? It hath been already of old time . . .'
Ecclesiastes, chap. I, v. 10.

The disadvantages of cortisone, prednisone and prednisolone helped to stimulate the search for the perfect steroid with potent anti-inflammatory properties but negligible side-effects. Triamcinolone ($\Delta^1, 9 \alpha$ fluoro-16 α hydroxy hydrocortisone) was synthesized by Bernstein *et al.* (1956) and preliminary reports indicated superiority over its predecessors. Three years' clinical experience have tempered this enthusiasm and indeed it is now recognized that use of triamcinolone may be attended by drawbacks which are unique in the steroid range of drugs.

Addition of a fluoride atom (to hydrocortisone) at position 9 α increases the anti-inflammatory effect over that of hydrocortisone seven times but also increases the sodium retaining effect to at least 50 times that of hydrocortisone. The addition of a double bond between carbon atoms 1 and 2 to form delta 9 α fluoro-hydrocortisone does nothing to lessen this salt retaining power. However, Bernstein found that adding an hydroxy radical at position 16 to this latter compound completely neutralized the salt and water retaining properties; indeed a sodium excretory effect was claimed.

Animal experiments showed that triamcinolone was 10 to 40 times more active than hydrocortisone and 3 to 12 times more active than prednisolone in reducing glycogen deposition in rats, in whom no hypertensive effect was observed. Rat studies also showed diuresis and increased excretion of sodium on triamcinolone, but potassium excretion was not increased beyond that of the control period even when the drug was given in 25 times the dosage used clinically. Furthermore over nine days no increase occurred in phosphate excretion—again with a very large dose of triamcinolone. Preliminary reports of metabolic studies in patients were presented at a meeting of the

American Rheumatism Association in November 1956, when the results bore out the impression from the animal experiments. However, it should be noted that the trials were relatively short term; in practice it is found that osteoporosis may develop only after a patient has been on a steroid drug for many months.

At this meeting triamcinolone was hailed by most workers as the best steroid of all, but it is salutary to note the comment of Dr. C. J. Smyth, who said, 'I cast the spell of extreme scepticism over an apparently euphoric audience after hearing about yet another steroid substance.' Obviously he was waiting for long-term trials which compared this steroid with others so that he could take account of its side effects. Prednisone and prednisolone have the advantage over cortisone of not causing salt and water retention; did this new steroid in its turn cause less osteoporosis than the others, and was it less likely to produce peptic ulcers with their attendant complications?

In 1958, Freyberg *et al.* (1958) published the results of long-term treatment with triamcinolone in 89 patients with rheumatoid arthritis, noting a good anti-rheumatic effect. They considered that it was extremely advantageous over prednisone in that it had very little tendency to produce peptic ulcers, but admitted that two of their patients developed severe osteoporosis. Other side effects were also mentioned: headaches, dizziness, light-headedness, sleepiness, flushing of the face and trunk, lack of appetite and weight loss—which were peculiar to triamcinolone. Their results were confirmed by Zuckner *et al.* (1958) in 50 patients. As a result of their trials it was thought that 4 mg. triamcinolone were equivalent to 5 mg. prednisone or prednisolone regarding anti-inflammatory properties. Again, from America, Hartung (1958) reported use of triamcinolone in 67 patients with rheumatoid arthritis, every one of whom showed unwanted side effects of some kind. Oedema and hypertension, however, did not appear and if patients had oedema following

treatment with prednisone, the oedema disappeared. Gastric symptoms were far less common and less severe than with the other steroids. Troublesome side effects made it necessary to stop the drug in 23 patients because of one or more of the following: weakness and fatigue (6); tachycardia (5); cramps (5); indigestion (5); recurrence of old duodenal ulcer (1); mental symptoms (4); headache (3); hirsuties (3); respiratory infection (1), but in no case did weight loss in excess of 10 per cent. of the original occur.

On the other hand, Hart *et al.* (1958), in their short-term trial on 24 patients with rheumatoid arthritis found that triamcinolone is just as likely to produce indigestion as prednisolone. Our experience at the Westminster Hospital confirms this and workers on this unit do not credit the drug as being less dangerous in producing ulcers than other steroids. Nevertheless it is a useful drug as there are certainly some rheumatoid patients who would prefer it to any other steroid both for its therapeutic effect and the absence of accompanying dyspepsia. One woman who had had prednisolone without ill effect for three years had a melaena on being changed to triamcinolone. Another patient, however, who had ulcer symptoms and a haematemesis with prednisolone has now received triamcinolone for 18 months with no dyspepsia whatsoever. Every rheumatoid patient is a law unto himself and it is very difficult to generalize about which particular steroid will suit an individual best.

Another point is worth comment. Hart *et al.* (1958) noted that three patients quickly developed abdominal striae within three weeks of changing to triamcinolone having had prednisolone for over two years. Three patients noted post-prandial flushing with triamcinolone. It is interesting to compare this with Dubois' work (1958) on systemic lupus erythematosus, when he noted that cutaneous side effects such as a Cushing-like appearance, striae and hirsutism became more marked than with the other steroids. The average dose was 26 mg. daily in divided doses—a dose which of course is considered to be more than double the maximum which can normally be given with safety, for example in rheumatoid arthritis or asthma.

Side effects following triamcinolone were emphasized by Kendall and Hart (1959); 24 of their 47 patients suffered side effects (the most common being facial and body flushing) and of these the drug had to be withdrawn in four. Severe weight loss was apparent in seven cases and rapid symmetrical muscle wasting in four. On the other hand clinical suppression of the rheumatoid disease was satisfactory and 36 patients continued to receive the drug with benefit.

Eight patients developed dyspepsia and in one there was gastrointestinal haemorrhage within 24 hours of indigestion beginning. Four patients had mental depression, and two had spontaneous fractures. However, in a dose of 6 mg. daily the authors concluded that there was almost complete freedom from side effects and that the drug was more effective than prednisolone in equivalent dosage.

In the very early trials with triamcinolone weight loss and weakness were reported, and these were noted also by Dubois who considered that 'triamcinolone is not the drug of choice in systemic lupus erythematosus.' For example, 11 of Freyberg's 89 patients complained of muscular fatigue. Williams (1959) investigated this interesting matter further and reported three cases where proximal muscle weakness followed triamcinolone treatment. In two cases muscle biopsy was done, demonstrating widespread damage, and in all cases myopathy was confirmed by electromyography. The weakness seemed at any rate, partially if not wholly reversible when the triamcinolone was stopped, and it was shown not to be due to hypokalaemia. Possibly the particular structure of triamcinolone potentiates this phenomenon, and indeed Maclean and Schurr (1959) have described a patient who developed a muscular paralysis on fludrocortisone, and who recovered from this when the drug was withdrawn. Fludrocortisone as well as triamcinolone possesses a fluorine atom in the 9-position. However, this is probably not the complete explanation, for Harman (1959) has observed a similar myopathy in patients treated with prednisolone, and Ellis (1956) was able to induce a widespread necrosis of skeletal muscle in rabbits when they were given large doses of cortisone. Of all clinical reports on triamcinolone Robinson and Robinson (1959) emphasize most strongly loss of weight: ten of their patients with rheumatoid arthritis lost weight, the average loss being 8 to 9 lb. It is fair to state however, that some of this may have been due to excretion of the water retained in the tissues following the use of other steroids. Our experiences at the Westminster Hospital agree with these findings and we consider that weight loss and weakness with triamcinolone are not rare. On the other hand they do at least have the virtue of being reversible and need hardly be regarded as a contraindication to a trial of this drug in any particular patient. In general, triamcinolone is of greatest use when there is cardiac failure or when a patient has become water loaded by the use of other steroids. It should not be used in Addison's disease or as replacement therapy in an adrenalectomized patient where cortisone is still the best choice.

Triamcinolone has been extensively used in dermatology. Again early reports were favourable; Kalz (1958) considered that various forms of severe dermatitis were better controlled with 6 mg. of triamcinolone daily than with 15 mg. of prednisolone. Rein (1957) came to a similar conclusion. Shelley *et al.* (1958) reporting its use in psoriasis found good suppression of the disease in a small dosage, whereas a much larger dosage giving rise to unwanted side effects was necessary when using prednisone or cortisone. In a short review of steroid therapy in skin diseases Bettley (1959) states that, '... at the present time prednisone is chiefly used, though perhaps before long triamcinolone will emerge as being somewhat superior.' Some dermatologists, however, are now favouring the newest steroid dexamethasone. It should be remembered nevertheless that patients with skin diseases may react differently as do those with rheumatoid arthritis, and Shelley *et al.* (1958) mention that occasionally a patient does better with prednisolone than with triamcinolone.

Summing up, triamcinolone should not be used for steroid replacement therapy. It has advantages over cortisone and prednisone if the patient is oedematous or in heart failure but against that, must be set the side effects outlined

above. Otherwise the drug is worth a trial in any patient intolerant of other steroids for no two patients react in precisely the same way.

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