group A gave higher antibody levels than 14 of the remaining 19 in the group, 3 of whom gave no response. In group B the primary responders gave antibody levels higher than some of the non-responders, whereas in group C this was not the case because the response to the booster dose was similar in both the primary responders and non-responders.

Discussion

These results of the responses of infants to a booster dose of vaccine give a clearer picture of the influence of maternally transmitted antibodies on primary immunization. High levels of such antibody completely inhibit active immunization against the homologous type. No infant with an antibody level of 1,024 or more before primary immunization gave a secondary response to the booster dose, indicating that primary immunization had been ineffective. This was true for all three virus types, although a high level of maternal antibody to one type had no inhibiting effect on the response to either of the heterologous types. Infants who had apparently not given a primary response, but whose secondary response was as good as that of the primary responders, had maternally transmitted antibody levels between 32 and 1,024; clearly these levels had not completely inhibited, but had merely masked, the primary response. Infants with low maternal antibody levels who had responded to primary immunization showed a good response to the booster dose. There were, however, a number who, in spite of the fact that they had low levels of transmitted antibody, did not respond initially — the "poor responders"—and these gave a similarly poor response to the booster dose.

It is also evident from the results that the best response is given by the 10-weeks-old infants, but these can by no means be regarded as satisfactory, and compare unfavourably, especially for type 1, with those obtained in 1- to 9-year-old children (Medical Research Council, 1957a, 1957b).

These results substantiate our initial conclusions that immunization in the first few weeks of life is unsatisfactory, especially to the type 1 virus. In order to be effective, primary immunization should produce substantial antibody responses to all three types in order to ensure an adequate secondary response to the booster dose. This is not likely to be achieved with existing vaccines unless immunization is delayed until the maternal antibody has fallen to a low non-inhibitory level, which may not be until the infants are 6 to 9 months old. These age groups are at present being studied.

Summary

A study was made of the effect of a third dose of poliomyelitis vaccine in a group of 80 infants who at the time of primary immunization were 10 weeks of age or less. The booster dose was given 10 to 12 months after primary immunization.

In 17 infants a rise in antibody titre occurred between primary immunization and the booster dose, indicating intercurrent poliomyelitis infection. These infants were excluded in assessing the effect of the booster dose.

Infants who showed an increase in antibody level after primary immunization also responded to the booster dose, but they all had low levels of maternally transmitted antibody. Those with high antibody levels at birth who gave no primary response did not react to

the booster dose. A number with intermediate levels of maternal antibody who showed no apparent primary response reacted to the booster dose; in these, primary immunization had evidently occurred, but the rise in titre was masked by the maternal antibody.

In general, the infants who had started their primary immunization at 10 weeks of age responded better to the booster dose than those starting at 1 and 6 weeks old.

This study confirms our original conclusion that immunization of infants against poliomyelitis in the first few weeks of life cannot be regarded as satisfactory, especially with regard to the response to type 1 virus. It is possible that the earliest age when satisfactory mass immunization may be achieved is when the infant is 6 to 9 months old. This age group is at present being studied.

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SIDE-EFFECTS FOLLOWING TRIAMCINOLONE

BY

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The initial reports on the use of triamcinolone (16 α -hydroxy, 9 α -fluorohydrocortisone) as a suppressive agent in rheumatoid arthritis were extremely encouraging. Originally announced by Hellman *et al.* (1957) at the American Rheumatism Association meeting at Bethesda in 1956, it was stated to possess powerful antirheumatic properties. They claimed that an average dose of 13.5 mg. daily resulted in a response superior to that observed with other steroids; metabolic balance studies suggested that little or no sodium retention or potassium or nitrogen loss occurred, and at that time no undesirable side-effects had been noted. Bunim (1957) agreed with these findings, but warned that it was much too early to draw any conclusions, as at that time only a few patients had been treated for short periods.

Later reports suggest that the side-effects normally associated with steroid therapy do in fact follow the prolonged administration of triamcinolone. Hollander

(1957), as well as being unable to confirm that the clinical potency of the drug was any greater, dose for dose, than prednisone or prednisolone, noted that, out of six patients observed, two experienced dyspepsia, three anorexia, and all lost weight. Three of his patients reverted to their original steroid because of increasing symptoms and signs of arthritis despite increased dosage. Dudley Hart *et al.* (1958) found that 2 out of 27 patients developed Cushingoid facies and striae, one suffered crush fractures of the ribs and lumbar vertebrae, three suffered from dyspepsia, and one had a perforated gastric ulcer. Three patients in his series suffered from "postprandial flushings" and one developed hypertension. They concluded that, although triamcinolone is a useful steroid, it does not differ greatly from prednisolone in its therapeutic action or in its undesirable side-effects.

Thus it appears that there still exists controversy over the relative potency of triamcinolone as well as over the incidence of side-effects in patients on long-term therapy. It was thought worth while, therefore, to report the clinical progress and side-effects observed in a series of 47 patients suffering from rheumatoid arthritis who have been treated continuously with the drug for periods varying from 5 to 11 months.

Selection of Patients

The two hospitals at which the present series of patients were treated lie in the centre of a densely

populated residential area, approximately 15 miles (24 km.) from the centre of London. As a result, many of the patients suffering from rheumatoid arthritis are living at home, having retired or been forced by the ravages of their disease to give up work. Furthermore, many of them have visited other specialist centres in the past, and undergone numerous forms of treatment. We are therefore only too frequently faced with the severely disabled and dispirited patient with overwhelming rheumatoid disease, often further complicated by visceral manifestations, who sits at home and loses all interest in life. We feel that the administration of steroids as a part of the medical treatment of selected patients in this group is essential if they are to be satisfactorily rehabilitated.

The majority put on to triamcinolone were already undergoing treatment with prednisone or cortisone, and were changed to the new drug either as a result of diminishing clinical response to increasing dosage or on the appearance of side-effects.

No special precautions were taken to prevent the patients knowing that they were on a new drug, the main object throughout being to obtain the maximum therapeutic benefit for each individual. Thus the observations made cannot in any way be said to result from a specifically controlled trial; they are nevertheless of value inasmuch as they relate to a special group of patients who have been treated for a longer period with the new steroid than any others so far reported.

Details of Patients in the Order in which they were put on to Triamcinolone

Case No.	Age	Sex	Duration of Disease	Mean Dose	Initial	Subsequent	Present Status	Total Period of Observation	Side-effects
1	63	M	4 years	16 mg.	Good	Well maintained	Continuing	11 months	Mooning, flushing
2	36	M	10 "	12 "	"	Deteriorated	On prednisone	10 "	Mooning, fractured ribs, flushing
3	58	M	16 "	12 "	Poor	Poorly maintained	Continuing	10 "	Mooning, dyspepsia, flushing
4	56	F	4 "	16 "	Good	Well maintained	"	10 "	Calf-wasting, flushing, mooning, loss of weight
5	39	F	5 "	4 "	"	" "	"	10 "	Nil
6	72	M	10 "	4 "	"	" "	"	10 "	"
7	59	F	1 year	4 "	"	" "	"	10 "	Depression
8	49	M	4 years	8 "	"	Deteriorated	On prednisone	7 "	Severe dyspepsia
9	31	F	11 months	8 "	"	Well maintained	Continuing	8 "	Flushing
10	83	F	14 years	4 "	"	" "	"	8 "	Nil
11	74	F	11 "	12 "	Poor	Improved	"	7 "	Loss of weight, dyspepsia
12	48	F	5 "	6 "	Good	Well maintained	"	7 "	Nil
13	63	F	13 "	8 "	"	" "	"	7 "	Flushing, mooning
14	75	M	2 "	4 "	"	" "	"	7 "	Nil
15	67	F	6 "	8 "	Poor	Improved	"	6 "	"
16	71	F	7 "	4 "	Good	Well maintained	"	6 "	"
17	30	F	4 "	4 "	"	" "	"	6 "	"
18	60	F	20 "	6 "	"	" "	"	6 "	"
19	50	F	1 year	8 "	Poor	Failed to respond	On prednisone	5 "	Mooning flushing, oedema
20	55	F	5 years	4 "	Good	" " " "	" "	6 "	Flushing, fractured metatarsal
21	43	F	5 "	4 "	"	Well maintained	" "	5 "	Nil
22	58	F	10 "	8 "	"	Deteriorated	On medrol	5 "	Dyspepsia, loss of weight
23	48	F	6 months	12 "	"	Well maintained	Continuing	6 "	Muscle-wasting, mooning, flushing
24	54	M	2 years	6 "	"	" "	"	6 "	Cushingoid, muscle-wasting, depression
25	46	F	8 "	6 "	"	" "	"	6 "	Nil
26	40	M	6 "	4 "	"	" "	"	6 "	"
27	68	F	13 "	4 "	"	" "	"	6 "	"
28	51	F	3 "	6 "	"	" "	"	6 "	"
29	53	F	5 "	6 "	"	" "	"	6 "	Flushing
30	47	M	20 "	4 "	"	" "	"	6 "	"
31	47	F	1 year	4 "	"	" "	"	6 "	"
32	64	F	20 years	4 "	"	" "	"	5 "	Flushing, loss of weight
33	42	M	6 months	4 "	"	" "	"	5 "	Nil
34	30	F	1 year	8 "	Poor	Poor response	Off steroids	5 "	"
35	62	F	3 years	8 "	Good	Well maintained	Continuing	5 "	Loss of weight, depression
36	72	F	24 "	12 "	Poor	Poor response	On prednisone	4 "	Mooning, dyspepsia, flushing
37	64	F	8 "	12 "	"	" "	On medrol	3 "	Cushingoid, calf-wasting, flushing
38	54	F	1 year	8 "	Good	Well maintained	Continuing	8 "	Flushing, depression
39	61	F	5 years	4 "	"	" "	"	5 "	Nil
40	27	M	7 "	8 "	"	" "	"	5 "	"
41	53	M	1 year	12 "	Poor	Improved	"	5 "	"
42	51	M	5 years	10 "	Good	Well maintained	"	5 "	Flushing
43	40	F	1 year	4 ", b.d.	Poor	Deteriorated	Off steroids	3 "	Nil
44	47	M	2 years	4 mg.	Good	Well maintained	Continuing	5 "	"
45	61	M	20 "	4 "	"	" "	"	5 "	Flushing, dyspepsia
46	31	M	8 "	12 "	"	" "	"	5 "	Flushing, mooning
47	54	F	12 "	8 "	"	" "	Off steroids	5 "	Haematemesis

As a rule each patient has been seen at fortnightly intervals, although in some cases the intervening periods have been longer, where patients lived some distance from the hospitals and their general practitioner was prepared to take over maintenance.

At each attendance a full subjective and objective assessment was made, being based on joint tenderness, joint range, and walking-time for a given distance. A detailed search for side-effects was carried out, and repeated examinations of the erythrocytic sedimentation rate and electrolytes were undertaken. Details of the 47 patients are given in the Table.

Results

Of the 47 patients who began treatment with triamcinolone, 36 are still maintained on the drug. Of the 11 who were taken off, seven had deteriorated rapidly, and four suffered from side-effects severe enough to merit cessation of the drug. Of those that deteriorated, six are now well maintained on prednisolone, two on 6-methyl prednisolone, and three have ceased steroid therapy altogether.

Altogether 24 patients have experienced side-effects: of these, the commonest is facial and body flushing, which occurred in 17 patients. The facial appearance is quite typical, and is distinct from that usually associated with high dosage of the other steroids. The skin of the whole face from the hair-line down to the neck appears to be involved, and becomes a uniform bright pink colour, the whole picture being so characteristic that it has merited the term "triamcinolone face" amongst the nursing and physiotherapy staff.

"Mooning" of the face was observed in nine patients; two of these exhibited marked hirsuties within six to eight weeks of starting treatment. Eight suffered from dyspepsia, and one of the latter developed haematemesis and melaena within 24 hours of the first symptoms of dyspepsia. Mental depression occurred in four patients, but in none was its character severe enough to merit stopping the drug. In two patients spontaneous fractures occurred. These were of the ribs and a metatarsal bone respectively; both had been on prednisone for a considerable period prior to the triamcinolone. Severe weight loss—more than 14 lb. (6.4 kg.)—occurred in five of the patients, and in four the phenomenon of rapid symmetrical muscle-wasting was observed. In three this involved predominantly the leg muscles, and in two the arms and shoulders. In all, these symptoms appeared within three months of commencing the triamcinolone, and in two the condition has deteriorated slightly on continued therapy; in the other two, muscle bulk and power have returned on reverting to alternative steroids.

With respect to the clinical suppression of the symptoms of the rheumatoid arthritis, 36 patients continue to be well maintained and are continuing with treatment despite the presence of minor side-effects in a small number.

Discussion

As with other observers, we agree that there appears to be little to choose between triamcinolone and other available steroids in relation to its potency in arthritis, particularly where high dosages are concerned. The incidence of side-effects following long-term therapy, however, seems to be as high as if not higher than that normally expected from prednisone. Only one patient

out of 11 on a dosage of 12 mg. daily or higher was free of side-effects after a period of five months or longer. The dangers of gastro-intestinal haemorrhage, and the chances of developing a Cushingoid syndrome or hirsuties, moonface, and facial flushing (see illustration) still appears to be as great as they are with prednisone or prednisolone.

Local muscle-wasting, the cause of which is rather puzzling, is a new complication to follow steroid therapy. K. S. MacLean (1958, personal communication) has reported a similar case following prolonged treatment with large doses of 9 α -fluorohydrocortisone, and suggests that the fluorine atom present in the 9 α -position in both drugs may be responsible for this property. The disability that results from this complication can be severe, and the problem obviously requires further elucidation. In our view the weight loss that sometimes occurs is not necessarily a handicap, for many of the patients we see are considerably overweight. It may well be that there is a place for alternating, say, prednisone

and triamcinolone over periods of one or two months to counterbalance the opposing tendencies of each drug.

Perhaps the most significant feature of the results obtained from the series so far is the relative lack of complications following the administration of 6 mg. or less of triamcinolone daily. Only three patients out of 23 on this dosage suffered any discomfort, and all continue to be well maintained on the drug. This dose has given a good clinical result in a considerable number of patients, and it is our impression that the response is much greater than that following the equivalent dosage of prednisone and prednisolone (5–7.5 mg.). It is our rule now to begin therapy on a dosage of 4 mg. daily, increasing it to 6 mg. if necessary, but avoiding greater dosages if possible. At present we feel that this is the highest level at which therapy can be safely prolonged. Only increasing experience will show whether serious side-effects will eventually follow this small dose. If they do not the fact that such a good clinical response can be obtained in this way will certainly make triamcinolone an extremely valuable drug in the treatment of rheumatoid arthritis.

Case 23. Cushingoid facies six weeks after starting on triamcinolone. Hirsuties also present.

Summary

The clinical progress of 47 patients treated with triamcinolone in doses of up to 16 mg. daily, for periods of up to 11 months, is reviewed.

Altogether, 24 patients had experienced serious side-effects, the majority of which resemble those seen following other steroids. Four patients suffered muscle-wasting, the causation of which is not obvious.

Of the patients receiving less than 6 mg. a day, only three suffered any discomfort, and it is suggested that this is the highest maintenance dose which can be prolonged.

We thank Dr. M. E. Fearnley, Consultant to the Physical Medicine Department, Orpington Hospital, Kent, for being allowed to report on his patients, and the pharmacists at both hospitals for obtaining supplies in the early stages. We are also indebted to the many local practitioners who have co-operated so willingly with us.

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CIRCULATORY EFFECTS OF TRUMPET PLAYING

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It is well known among professional trumpeters that playing high loud notes for more than a few seconds may cause dizziness or occasionally "black-out." Indeed, many leading orchestras carry an assistant or "mate" to take over from the first trumpet in prolonged difficult passages. All are agreed that Wagner is the composer with least consideration for the feelings of the trumpet player. The mechanisms causing dizziness appear obvious, but it seemed worth while to obtain continuous records of the pressures blown and their consequent circulatory effects, since observation suggested that greater pressures across the vibrating aperture were needed in trumpet playing than in any other commonly used instrument.

Material and Methods

The measurements were made on one of us (M.F.), who is a professional player and teacher of the trumpet. Some measurements were also made on two other subjects: an amateur surgical colleague, who played in the Cambridge University dance band 30 years ago, and a novice member of the department who purports to be learning the oboe. Pressures were measured with capacitance manometers, mouth pressure with a fine water-filled "polythene" tube, and intrathoracic pressure in the oesophagus (Dornhorst and Leathart, 1952). The trumpet was held and played with the right hand, while arterial pressure was recorded in the left brachial artery.

Results

As expected, the circulatory effects of trumpet playing are similar to the effects of the Valsalva manoeuvre. Fig. 1 shows the professional playing Concert A moderately loudly for 17 seconds. The pressure blown is about 80 mm. Hg, or a good deal higher than the 50 mm. Hg normally used to test the circulation (Sharpey-Schafer, 1955). The subject maintains a relatively constant pressure in producing his note, yet very few normal subjects are capable of

blowing a mercury manometer to this height and maintaining it at a constant level without extensive practice. The effects on the circulation are those of a formidable Valsalva manoeuvre: peripheral venous valves shut and blood accumulates distal to them. The effective cardiac-filling pressure, stroke output, and mean arterial pressure fall off rapidly. After about 7 seconds the slight rise of arterial pressure indicates the onset of reflex constriction, which persists, after cessation of blowing, during the overshoot. Since the brain is not protected by venous valves the supply pressure across it falls so that the cerebral blood flow may become inadequate during the period of blowing. More usually dizziness or black-out is maximal immediately on release of intrathoracic pressure, as occurred on the occasion of recording Fig. 1.

In Fig. 2 the professional is shown blowing a loud arpeggio up to high D. On the top note he reached a pressure of 160 mm. Hg. Thereafter he blew a series of rapid blasts which produced rapid transients on the arterial pressure curve. In Fig. 3 he is playing a long phrase from Wagner at a relatively low pressure; circulatory changes are still conspicuous. It is interesting to compare the performance of the amateur and the novice with that achieved by the professional.

FIG. 1.—Professional player blowing Concert A for 17 seconds. Upper curve, arterial pressure. Lower curve, mouth pressure. Calibration in mm. Hg and time marker in seconds in this and subsequent figures.

FIG. 2.—At the first arrow an arpeggio is blown to high D (160 mm. Hg mouth pressure). At the second arrow a series of rapid blasts are blown for 6 seconds.

FIG. 3.—A long (28 seconds) phrase is played from *Tannhäuser* without drawing breath.