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Posterior Subcapsular Cataracts as a Complication of Adrenocortical Steroid Therapy

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BLACK, Bunim *et al.* recently reported the discovery of posterior subcapsular cataracts (PSC) in many patients with rheumatoid arthritis receiving corticosteroid therapy.[1] They interpret this as representing a hitherto unrecognized complication of adrenocortical steroid therapy. They reported that PSC occurred more frequently in male than female patients; that it was not observed in 19 patients with rheumatoid arthritis who had not received corticosteroid therapy, or in those on a low dosage or who had received hormonal therapy for less than a year; but that it was apparent in 30% of a group of 44 rheumatoid arthritis patients who had received corticosteroids for a long period. A statistical correlation, which was highly significant, was found between the development of PSC and the use of moderate or high maintenance dosage of corticosteroid preparations for longer than a year.

Subsequent formal publications[2, 7] on this subject in the medical literature to date have been few, but brief references have been made to similar (unpublished) studies in other centres that have not tended to confirm any specific relationship of PSC with corticosteroid therapy.[3a, 3b, 3c] Apparently all these studies, like the original one, have concerned themselves almost exclusively with patients receiving corticosteroid therapy for rheumatoid arthritis.

So far as non-rheumatoid populations are concerned, the only available information is from Gordon, who is quoted[5] as referring to studies of several smaller series of non-rheumatoid cases treated with high doses of steroids, and finding a PSC incidence of $< 4\%$ among a total of 92 cases. He is quoted as suggesting that this is about equal to the incidence of PSC in the "normal" population.

If the reported high incidence of PSC in rheumatoid cases is confirmed by further observation (which has not been entirely the case[3c]), it might, of course, be causally related to the disease process *per se*, and only fortuitously to the steroid treatment for that disease. Black, Bunim *et al.* consider this possibility and attempt to rule it out by comparing a control (non-steroid-treated) rheumatoid group with a treated group. However, the value of such a control group is nullified for this purpose when one considers the fact that a direct correlation must be expected between the severity of the rheumatoid process and the incidence, intensity and duration of steroid therapy. Lens lesions of this type, sometimes characterized as "complicated cataract", and considered to be a change secondary to degenerative disease of the eye, might be related to the well-known tendency for rheumatoid arthritis to be more or less frequently complicated by uveitis or iritis. On the other hand, in the absence of such specific rheumatoid ocular disease, PSC might be related in some non-specific fashion to the severity of the rheumatoid arthritic process (which is not necessarily correlated with the ocular lesion *per se*).[6] A possible mechanism for such non-specific damage might lie in the location of the lesion. PSC is anatomically localized to that portion of the crystalline lens which is most remote from the circulation and/or actively metabolizing cells: a location which is considered to be peculiarly vulnerable to metabolic stresses.

With these considerations in mind, and because of the obvious clinical significance of this observation, we have searched for PSC in 56 patients who had received corticosteroid therapy for varying lengths of time for conditions other than rheumatoid arthritis. Fifty-three of these had bronchial asthma, but did not have rheumatoid arthritis; two had the nephrotic syndrome; one had both bronchial asthma and a form of arthritis which had been tentatively diagnosed as rheumatoid arthritis, but was very atypical. The results are reported herewith.

METHOD

All patients were examined by ophthalmologists (C.D. and C.A.T.) using ophthalmoscopic and slit lamp techniques after dilatation of the pupil. The examining ophthalmologist was not informed at the time of the examinations as to whether the patient had received steroid therapy at all, or as to the dosage and duration of such therapy. Those cases with positive findings were recalled for a second eye examination at a later date, and for appropriate laboratory tests to rule out diabetes mellitus and hypocalcemia. Appropriate clinical history and physical examination ruled out myotonia and atopic dermatitis. These latter four systemic conditions had been reported to be occasionally associated with the development of posterior subcapsular opacities.[1]

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TABLE IA.—OCULAR CONDITIONS PRESENT IN 56 PATIENTS TREATED WITH CORTICOSTEROIDS

PSC	*Patient*	*Ophthalmological findings*	*% of group*
Positive	R.W.*	Spoke-shaped haziness in the cortex of each eye and slight PSC changes.	5.4
	R.L.*	Lenticular subcapsular changes in region of equator as well as posterior pole. Increased density minimal, but more than expected in man of 29.	
	S.M.*	Minimal (and equivocal) posterior subcapsular changes in the right eye.	
Negative	F.M.	Traumatic cataract in the right eye predating steroid therapy.	
	R.J.	Angiomatosis retinae predating steroid therapy.	
	R.D.	Minimal early Fuch's dystrophy of cornea.	
	R.L.	Bilateral corneal scarring, probably due to childhood keratitis.	
	A.C.	Old chorioretinitis.	
	I.B.	Marked bilateral senile cataracts with gross loss of vision, predating steroid therapy and progressing gradually.	
	E. McM.	Two posterior cortical punctate opacities antrally, presumably congenital, not resembling PSC.	
	G.B.	Few punctate lens opacities, undoubtedly congenital.	
	D.S.	Few small "snow flakes", but no PSC.	
	D.F.	Few fine discoid opacities and poorly demarcated spokes of haze are seen in the periphery of both lenses—"within normal limits".	

*See appendix for case summaries.

None of these patients had uveitis, high myopia, retinal detachment or retinitis pigmentosa: conditions which are said[1] to produce lenticular opacities that sometimes resemble closely the type of lenticular change under study here. Previous exposure to diagnostic and/or therapeutic radiation was evaluated in all these patients by review of their hospital x-ray files supplemented by personal communications from the patients.

TABLE IC.—NON-OCULAR CONDITIONS DIRECTLY RELATED TO CORTICOSTEROID TREATMENT

Diagnosis	*No. of cases*	*% of group*
Moon facies	21	37.5
Dyspepsia	7	12.5
Hypomanic stimulation	4	7.1
Excessive bruising	4	7.1
Hypertension (steroid-induced)	4	7.1
Post-steroid obesity	3	5.4
Peptic ulcer (steroid-induced)	2	3.6
Growth inhibition	1	1.8
Osteoporosis of spine (with collapse fractures)	1	1.8
Peripheral edema	1	1.8
Hirsutism	1	1.8
Addisonian collapse (postoperative)	1	1.8

OBSERVATIONS

1. As noted in Table 1A, PSC was found in three cases of the 56, two definite and one doubtful. This constitutes 5.4% of the group examined. The number is so small that ordinary chi square tests of statistical significance cannot be applied. However, some general comments can be made. Many other diseases (listed in Tables IA to ID) were observed to co-exist in these patients, some being related and some obviously unrelated to either the bronchial asthma or the corticosteroid therapy. Some of the latter conditions, such as arterioscler-

TABLE ID.—NON-OCULAR CONDITIONS INDIRECTLY RELATED TO CORTICOSTEROID THERAPY

Diagnosis	*No. of cases*	*% of group*
Moniliasis	2	3.6
Pneumonia with lung abscess	1	1.8

TABLE IB.—NON-OCULAR CONDITIONS NOT OBVIOUSLY RELATED TO CORTICO-STEROID THERAPY

Diagnosis	*No. of cases*	*% of group*	*Diagnosis*	*No. of cases*	*% of group*
Bronchial asthma	54	96.4	Auricular fibrillation	1	1.8
Hypertrophic sinusitis	9	16.1	Hypometabolism (thyroid)	1	1.8
Chronic psychoneurosis	8	14.3	Osteoarthritis	1	1.8
Nasal polyposis	4	7.1	Mental deficiency	1	1.8
Chronic respiratory insufficiency	4	7.1	Vascular headache	1	1.8
Arteriosclerotic heart disease	4	7.1	Goitre	1	1.8
Essential hypertension	3	5.4	Gout	1	1.8
Primary obesity	3	5.4	Chronic cholelithiasis	1	1.8
Emphysema	3	5.4	Acute cholecystitis	1	1.8
Pneumonia	3	5.4	Reactive depression	1	1.8
Irritable colon	2	3.6	Hypothyroidism (due to iodide therapy)	1	1.8
Nephrotic syndrome	2	3.6	Tonsillitis	1	1.8
Aspirin allergy	2	3.6	Peripheral neuropathy	1	1.8
Acute respiratory insufficiency	2	3.6	Toxemia of pregnancy	1	1.8
Atopic dermatitis	2	3.6	Lung fibrosis	1	1.8
Migraine	2	3.6	Osteoarthritis of spine	1	1.8
Penicillin allergy	2	3.6	Barbiturate allergy	1	1.8
Tetracycline allergy	2	3.6	Graves' disease	1	1.8
Uterine prolapse with cystocele and rectocele	2	3.6	Ragweed hay fever	1	1.8
Rheumatoid arthritis	1	1.8	Myotonia	0	0
Diabetes mellitus	1	1.8	Hypocalcemia	0	0
Coronary thrombosis	1	1.8			

otic heart disease, were more common than PSC, yet cannot be reasonably attributed to the steroid therapy *per se*. Other conditions, such as cushingoid facies, peptic ulcer and osteoporosis, are well known to be directly due to hypercortisonism. The acute manifestations of hypercortisonism, e.g. moon facies, occurred as one might expect, quite frequently in the group, but other chronic manifestations, such as osteoporosis, occurred like PSC, with quite a low frequency. This emphasizes the fact that even though PSC is an infrequent finding in the group, this *per se* does not rule out the possibility of a direct causal relationship to the steroid treatment.

However, if PSC were, in fact, a lesion produced by excessive and/or prolonged steroid treatment, one might expect to find it in conjunction with other lesions well recognized as late complications of steroid treatment. PSC was *not* found in the ten patients who manifested those complications (Table IC): hypertension, post-steroid obesity, peptic ulcer, stunted growth, osteoporosis with vertebral collapse. The three cases with PSC had none of the known complications of steroid therapy. One of these cases (D.L.) had received only 2.5 g. of prednisone over a 26-week period. Several of our cases with known steroid-induced complications had taken total doses of this same order (2.59.); but in each instance the total was the result either of much larger doses taken over a much shorter period or smaller doses taken for a much longer period. Seventy-five per cent of them had taken larger doses for a much longer period than 26 weeks; the average treatment period was 123 weeks.

2. The age and sex distribution of the group are listed in Tables II and III. PSC was observed in both male and female patients, but it is difficult to draw any conclusions about the sex distribution of PSC on the basis of this small sample. It may be noteworthy that, except for six children, the two male subjects with definite PSC were the only subjects in the group below 31 years of age.

TABLE II.—POSTERIOR SUBCAPSULAR CATARACTS AND THE AGE OF 56 PATIENTS

Age in years	*Positive PSC*	*Negative PSC*	*Total*
<15	0	6	6
15 - 40	2*	17	19
40+	1 (?)†	30	31
Total	3	53	56

*Ages 29 and 30 years.
†In this and subsequent Tables patient S.M., in whom the diagnosis of PSC was equivocal, is indicated in this manner.

TABLE III.—POSTERIOR SUBCAPSULAR CATARACTS (PSC) AND THE SEX OF 56 PATIENTS

Sex	*Positive PSC*	*Negative PSC*	*Total*
Male	2	21	23
Female	1 (?)	32	33
Total	3	53	56

TABLE IV.—POSTERIOR SUBCAPSULAR CATARACTS (PSC) AND THE DURATION OF CORTICOSTEROID TREATMENT

Duration of treatment (weeks)	*Positive PSC*	*Negative PSC*	*Total*
<50	1	15	16
50 - 150	1 + 1 (?)	28	30
151 - 300	0	10	10
Total	3	53	56

3. The cumulative steroid dosage up to the time of the initial eye examination is recorded in Fig. 2. Often, of course, long duration and high intensity of treatment vary together to increase the total steroid dosage for individual patients, but this is not always the case. Therefore duration and intensity are further considered separately. Duration of steroid therapy is outlined in Table IV. Intensity of steroid therapy is outlined in Table V, as expressed by the maximum 24-hour steroid dosage required to control particular exacerbations of acute status asthmaticus in a given patient; and in Fig. 1, in terms of the maintenance dose of steroid usually required each day to keep the patient's symptoms under control. This latter dose varies from time to time, but the dose recorded here is that which each patient used for most of the weeks of the one to five years prior to the date of this study. A close correlation cannot be demonstrated between long duration (Table IV), high intensity (Table V and Fig. 1) or total steroid treatment (Fig. 2) and the occurrence of PSC. The relationships between PSC and steroid dosage which are apparent in the rheumatoid group of patients[1] are not obvious in our patients.

TABLE V.—POSTERIOR SUBCAPSULAR CATARACT (PSC) AND THE INTENSITY OF CORTICOSTEROID TREATMENT

Maximum dose in mg. of Prednisone/day	*Positive PSC*	*Negative PSC*	*Total*
<30	0	12	12
30 - 60	1	36	37
61 - 100	1 + 1 (?)	5	7
Total	3	53	56

4. Incipient radiation cataracts are indistinguishable from the lesions described here. The type of radiation (nuclear explosion) producing such cataracts has not been experienced by this group of patients. However, in any radiological procedure involving the portion of the body above the diaphragm, some degree of exposure of the eye may occur and conceivably contribute to the development of PSC. A precise estimate of the radiation exposure of these patients is impossible because of the variance due to different apparatus, techniques, etc. The use of the formula developed by Ritter and colleagues[4] is not applicable outside the limited confines of their own study, unless checked and corrected in the manner which they suggest. Although it has been used in this context,[1] we do not consider that it really provides, in uncorrected usage, an estimate of past radiation exposure which

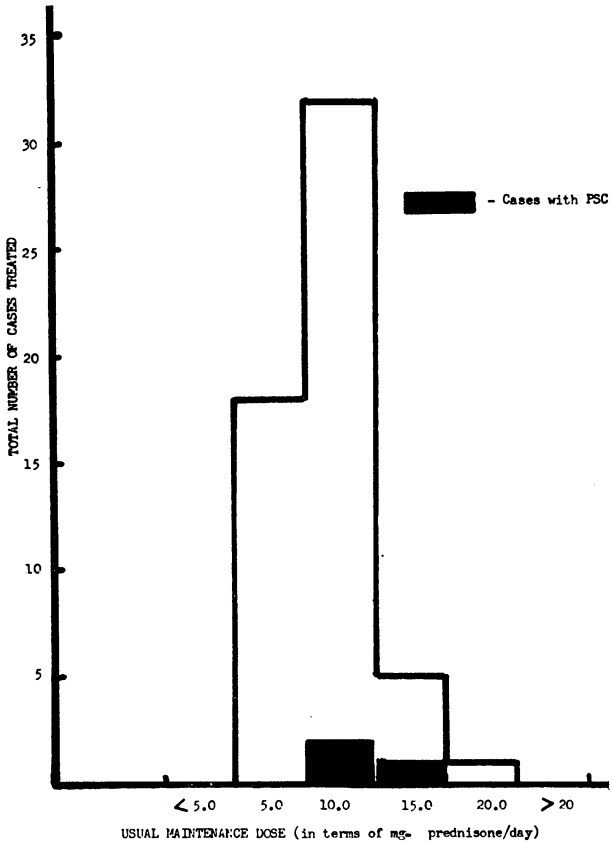

Fig. 1.—The distribution of usual maintenance steroid dose among 56 cases.

is any more meaningful than can be obtained by a simple summation of past radiologic procedures. This we have recorded in Table VI, using only

TABLE VI.—POSTERIOR SUBCAPSULAR CATARACT (PSC) AND DIAGNOSTIC RADIATION EXPOSURE

Total No. of radiographs of areas above the diaphragm	*Positive PSC*	*Negative PSC*	*Total*
<15	0	24	24
15 - 35	0	26*	26
>35	2 + 1 (?)	3	6
Total	3	53	56

*One patient had therapeutic radiation as well—dosage unspecified, with Grez radiation.

those patients for whom sufficiently reliable information could be obtained from local hospitals and radiologists. There would appear to be a positive correlation between amount of diagnostic radiation and PSC. However, these figures inevitably contain such a wide range of variation in actual roentgen exposure that they cannot be viewed as any more than a very approximate estimate of the desired data—and conclusions drawn from them are correspondingly subject to large error. Since, as Bunim has emphasized,[1] the total exposure with all these procedures is still much smaller than that required to induce cataract formation experimentally, it seems most unlikely that the genesis of PSC lies in diagnostic radiation exposure.

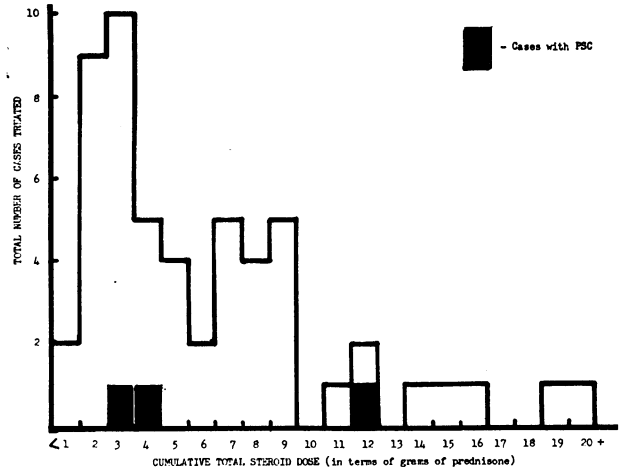

Fig. 2.—The distribution of total steroid dosage among 56 cases.

SUMMARY

We have found posterior subcapsular lenticular cataracts in 5.4% of a group of 56 patients being treated with adrenocortical steroid for chronic diseases other than rheumatoid arthritis. PSC would therefore appear to be much less frequent in this group than in steroid-treated patients with rheumatoid arthritis.[1] The only factor with which it appeared to correlate in this series was the number of diagnostic x-ray procedures previously performed on the patient.

The infrequency of PSC in these patients, and the lack of obvious correlation between its occurrence and the intensity and/or duration of adrenocortical steroid therapy, or with the occurrence of other well-recognized corticosteroid-induced complications or "side effects", would suggest that the occurrence of PSC is probably not, in fact, attributable to the steroid therapy itself. We interpret our findings as tending not to substantiate the original report[1] that PSC is a complication of steroid therapy. However, retrospective studies of this type can yield only a limited amount of information on a question like this. It is generally recognized that subject-drug interaction appears to play a large role in the occurrence of specific complications of corticosteroid therapy. This belief was confirmed in the present group of patients when we attempted to relate the occurrence of osteoporosis, etc. to the same parameters mentioned in regard to PSC, i.e. duration and intensity of steroid treatment, etc. A simple direct relationship could not be demonstrated; that is to say, while these "catastrophic" complications occurred in only those cases treated with a high dosage or of long duration, many other cases with a higher daily dosage or longer periods of treatment were, nevertheless, free of similar complications. We feel that long-term follow-up studies of controls and steroid-treated patients with various diseases are advisable in order to clarify the issue. Such studies might profitably direct special attention to those patients, already manifesting other complications known to be due to long-term steroid usage, to see whether PSC can be found more frequently in such individuals.

From a practical standpoint, in a fairly large group of asthmatic and nephrotic cases, treated for long periods (up to five years) with maintenance doses of steroids, PSC was found with a frequency not obviously different from that said to obtain in the non-

steroid treated "normal" population; and no visual symptoms attributable to PSC were found at all. There seems to be no reason to withold corticosteroids where their use is indicated because of fear of crystalline lens complications. Their indiscriminate use is, of course, never to be condoned.

APPENDIX

CASE SUMMARIES

R.W., a 30-year-old male, had had perennial mixed intrinsic and extrinsic asthma since September 1957. Respiratory infections caused intermittent disability, but the patient's symptoms were well controlled usually by continuous corticosteroid and bronchodilator drug therapy. He required 20-25 mg. of prednisone daily for many months, but now generally uses 10-15 mg. daily. The paranasal sinuses are normal. He had a course of desensitization lasting for three years which gave some seasonal protection.

R.L., a 28-year-old male, had continuous, progressive, totally disabling mixed intrinsic and extrinsic asthma which began in April 1952 in Japan. There was no family history of allergy. He was allergic to tetracycline (Achromycin) and penicillin, and had chronic sinusitis and a normal blood pressure. He relies on adrenaline and bronchodilator tablets. He was unresponsive to pollen, dust, and vaccine desensitization, and to several trials of intravenous ACTH and corticosteroid therapy in doses of up to 90 mg. of prednisone or 12.0 mg. of dexamethasone daily.

S.M., a 50-year-old female, had mild recurrent bronchitis since childhood and had periodically disabling intrinsic type (infective) asthmatic bronchitis for five years. She had arthritis which involved one elbow and the fingers between 1947 and 1955. This arthritis was extensively investigated and labelled probable rheumatoid (but very atypical). The patient had taken unknown, but probably small, amounts of corticosteroid intermittently for 10 years for these complaints. She was *in extremis* because of status asthmaticus one year ago and required intravenous ACTH and up to 100 mg. of prednisone daily. She has had continuous maintenance steroid therapy since, in a dosage of about 10 mg. of prednisone daily.

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