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LONG-TERM CORTICOSTEROID THERAPY AND ITS EFFECT ON THE KIDNEY

By

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The urinary disturbances due to prolonged corticosteroid therapy observed by us several years ago (9) do not appear to have given rise to very many clinical studies. In this report, we have therefore wished to outline the facts observed in a group of our patients who underwent systematic renal and urinary examinations.

MATERIAL AND METHODS

1 - 102 Patients

- 37 females and 65 males.
- suffering from chronic bronchitis or asthma were studied:
- their age distribution was as follows:

30 to 39 years: 5 patients
40 to 49 years: 14 patients
50 to 59 years: 39 patients
60 to 69 years: 33 patients
70 to 79 years: 11 patients

- these patients had been given one to two corticosteroid tablets daily (most frequently Methyl-Prednisolone or Triamcinolone):

32 of the for 1 to 5 years
65 of them for 5 to 10 years
5 of them for more than 10 years.

2 - *The Biological Examinations*

performed were as follows:

- 124 check-up examinations comprising:

- . Blood urea nitrogen test and test for albinuria
- . Urea concentration test
- Addis-Hamburger Count
- . Urine culture.

- 20 patients also had:

- . functional tests (clearances)
- . an urography

- finally, 8 histological examinations of the kidney were performed

- . 4 after death of the patients
- . 4 by needle biopsy of the kidney with optical and electronic microscopic examination.

RESULTS

1. *Clinical*

No urinary or renal lesion, especially of the infectious type, were found during the various consultations.

2. *Biological*

The facts observed were as follows:

- 70 Addis counts performed in 53 patients were normal or revealed only minor abnormalities (output less than 3 000 cells per mn).
- 54 counts performed in 53 patients were abnormal
 - . 10 times, it was a case of isolated leucocyturia
 - . 44 times, this was combined with microscopic hematuria, although to a lesser degree.
- the overall results were as follows:

<i>Addis Counts</i>		Positive
Number of blood cells	Number of patients	Urine culture Collibacillus
less than 3 000	70	3
3 to 5 000	20	2
5 to 10 000	13	2
10 to 50 000	18	4
more than 50 000	3	2

21 times the Addis count showed considerable alteration; details of the abnormalities involved are given in the following table:

White Blood Cells	Red blood Cells	Positive urine culture
7 428	19 984	+
10 080	1 120	
10 137	3 696	
10 920	32 760	
6 624	11 040	
12 100	6 300	+
13 600	42080	
16 800	370	
18 700	17 000	
20 216	577	
20 746	1 500	
21 000	328	
22 048	4 732	
31 204	1 164	+
33 600	4 800	
37 600	1 600	
40 800	1 600	
44 800*	3 360	+
74 212	8 646	
76 524*	8 650	+
126 000	13 500	

- finally, the other biological and X-ray examinations remained constantly normal; only once was a functional abnormality noted in an intra-venous urography performed in a patient presenting biological signs of urinary infection.
- the histological examinations of the kidneys revealed no abnormality attributable to corticosteroids, either in optical or electronic microscopy; only minor vascular lesions were observed, considered normal in view of the age of these patients.

Two examinations were performed in patients presenting a positive urine culture and a highly pathological leucocyte output: no lesion suggesting an infectious attack could be detected.

DISCUSSION

A. To understand the exact significance of the abnormalities of the Addis Count observed in our patients, we performed the same test in a control population of identical age, without any renal lesion and receiving no corticosteroid treatment. The mean result produced about 3 000 per mn. Our results therefore appear to be abnormal, since 21 of our patients, *i.e.* 20 per cent had an output per mn of more than 10 000 cells. (The leucocyte output was higher than 10 000, 19 times). Age does not appear to have been a determining factor, as indicated in the following table:

Age Range	Number of patients studied	Number of abnormal tests
30 to 39	5	0
40 to 49	14	4
50 to 59	39	7
60 to 69	33	7
70 to 79	11	3

Neither does the effect of the duration of corticosteroid therapy appear to be very evident, on the contrary.

32	70
Less than 5	More than 5
years' treatment	years' treatment
10	11
very abnormal	very abnormal
counts	counts

B. *What is the significance of these pathological results?*

a) The first hypothesis suggests the nephrotoxic effect of corticosteroids.

A number of authors became interested in this problem after *Rich* (19), in 1950, first observed the modification, under the effect of corticosteroids, of renal lesions induced by experimental anaphylactic reactions. *Bencosme* (3) and *Ashburn* (2) demonstrated that in animals, the corticosteroids produced lesions of the endothelial and epithelial cells. *Bouisson* (5), (6), (7) reproduced identical changes experimentally: he noted the occurrence of vascular dilatation and of thickening of the mesangium axis and confirmed the transformation of this lesion into a nodule of the Kimmelstiel-Wilson type observed in diabetic patients.

Moreover, some authors (10) (23) considered the possible role of hypercorticism as a pathological factor in producing the Kimmelstiel—Wilson nodule. In clinical conditions, *Oppenheimer* (15), (16) also observed the occurrence of such lesions during nephrotoxic syndromes treated with corticosteroids for a sufficient length of time.

It should be noted, however, that the lesions produced:

- nearly always occur in patients with a past history of renal disease and furthermore that they are erratic (18).
- are induced by heavy dosages, or at least by much larger ones than those given to our patients.
- are not specific, since corticosteroids favour the occur-

rence of a Kimmelstiel—Wilson nodule, accelerate certain processes such as amyloidosis (17), (21) and potentiate the effects of some nephrotoxic substances (20).

What has to be determined in the last analysis is whether or not the corticosteroids have a toxic effect on a previously sound kidney.

Recently, in the course of Cushing's syndrome, *Arkenbout* (1) did not find any specific lesion in his patients. However, in 4 out of a series of 11 children treated for an extra-renal affection, *Oppenheimer* (15) noted the absence of a Kimmelstiel—Wilson nodule, but the existence of lipoid "droplets" located in Bowman's capsule, near the afferent arteriole. This lesion which is predominant in the glomerules nearest to the medulla, also exists in patients with renal disease treated with corticosteroids. The author considers this lesion to be the most specific.

Despite our investigations, these "capsular drops" were not encountered in our patients, but it should be noted with *Oppenheimer* that these lesions are erratic and fragmentary and that they are not necessarily reached by renal biopsy.

Finally, the relation between this lesion and a pathological leucocyturia or hematuria hardly seems conceivable.

B. Thus, the second hypothesis which appears to be the most plausible is that of a latent urinary infection. It is true that this opinion is not shared by all the authors and recently *Wood* (22) observed that the existence of a bacteriuria was no more frequent in asthmatic patients given corticosteroids than in a normal population. However, it is well-known that in the course of urinary infections, bacteriuria is apt to be intermittent and repeated tests should be made (11).

Similarly, a close relation does not always exist between bacteriuria and leucocyturia. *Katz* (12), (13) and *Little* (14) therefore advocate the administration of corticosteroids to demonstrate the existence of a urinary infection; the effect of the corticosteroids is to increase the leucocyturia considerably, if the test is positive; this confirms our results.

Finally, measurement of the output per mn. of germs in the urine, according to Kass' technique, may afford more accurate knowledge of the significance of positive urine cultures and enable the site of infection to be identified with greater accuracy.

CONCLUSION

Urinary and renal examinations were performed in 102 patients, with chronic bronchitis or asthma, subjected to long-term corticosteroid therapy.

In 49 patients, a pathological increase in the leucocyte output was found, often coupled with microscopic hematuria.

In 13 patients, colibacilli were found in the urine culture test.

8 histological examinations of the kidney were performed. In contrast with other authors, we found no lesion in optical or electronic microscopy. The reason for this may be that our patients receive only low dosages of corticosteroids, whereas the nephrotoxicity of corticosteroids is only apparent with high dosages; as regards the abnormal increase in output per minute of red and white blood cells, this may be due to sub-clinical urinary infection.

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