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Fasc. 15 = Adv. Tuberc. Res. / Fortschr. TuberkForsch. / Progr. Explor. Tuberc. Vol. 10
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Fasc. 18 = Lungen- und Brustfellerkrankungen in Praxis und Klinik
Fasc. 19 = Adv. Tuberc. Res. / Fortschr. TuberkForsch. / Progr. Explor. Tuberc. Vol. 13
Fasc. 20 = Aktuelles aus Diagnostik und Therapie der Lungenerkrankungen
Fasc. 21 = Adv. Tuberc. Res. / Fortschr. TuberkForsch. / Progr. Explor. Tuberc. Vol. 14
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Index

A Critical Evaluation of Corticosteroids in Tuberculosis

By N.W. Horne, Edinburgh

A View of Tuberculosis Morbidity and Mortality Fifteen Years after the Advent of the Chemotherapeutic Era, 1947–1962

By Anthony M. Lowell, Atlanta (Georgia)

Bactériologie de la tuberculose ostéo-articulaire sous chimiothérapie

De A. Debeaumont, Berck Plage

Chapitre I

Considérations théoriques

Chapitre II

Pénétration des antibiotiques dans les lésions

Chapitre III

Bactériologie des lésions traitées

Chemotherapy and Chemoprophylaxis of Tuberculosis in Cattle

By H. H. KLEEBERG, Onderstepoort (South Africa)

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A Critical Evaluation of Corticosteroids in Tuberculosis

N.W. Horne*

Index

Introduction

The use of corticosteroids in tuberculosis has always been surrounded by controversy and even although there is now an extensive literature on the subject—some of it vague and uncontrolled, much of it detailed, scientific and thoughtful—the problem of the value of corticosteroids in the treatment of tuberculosis remains a complex one. The dilemma is well expressed in a letter written by Weiss [1963], in which he states: "Probably every phthisiologist has had the experience of seeing appar-

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ent reversal of the downhill course in an occasional patient with serious tuberculosis when corticosteroid hormone has been added to the therapeutic regimen in the absence of other changes in treatment. A few patients may have insufficient endogenous hormone to turn the tide in their favour even in the presence of adequate antimicrobial therapy. But this observation does not grant the physician license to use the hormones without discrimination. While it is true ... that no untoward effects attributable to the corticosteroids (were observed) this has not been a universal finding, and drug toxicity has to be given serious consideration by any practitioner who uses these hormones in doses sufficient to give an observable effect."

In the early days of corticosteroid therapy, concurrent anti-tuberculosis chemotherapy was not administered, and the reports of the development of tuberculosis—sometimes in florid form—in patients under treatment with corticosteroids engendered such alarm as to cause the AMERICAN TRUDEAU SOCIETY [1952] virtually to place an interdiction on the use of these hormones in tuberculosis. The Committee on Therapy stated: "At this time cortisone and corticotrophin appear to have no place in the treatment of active tuberculosis as such."

Discussing the treatment of tuberculosis, the BRITSH MEDICAL JOURNAL [1951] stated: "Among therapeutic possibilities it might be suggested that cortisone or tuberculin could be used to flush the bacilli from the lesions while streptomycin and PAS shoot them down. To employ such speculative manoeuvres would require great faith in the discrimination of the beaters and the accuracy of the guns." To continue the metaphor of the grouse-moor, the guns have become exceedingly accurate, particularly since the advent of isoniazid, so much so that the discrimination of the beaters is of less importance—unless the beaters flush out the tubercle bacilli when the guns have run out of ammunition. For in the subsequent two years, chemotherapy became very much more effective and several authors—particularly COCHRAN [1954]; EVEN, SORS, TROCME and SARRAZIN [1954]; EVEN, SORS, DELAUDE, ROUJEAU, TROCME and COMMARE [1955]; FAVEZ [1954]; HOUGHTON [1954] and TURIAF [1954]—reported that they were impressed by the favourable results obtained with a combination of corticosteroids and chemotherapy. Corticosteroid therapy in tuberculosis having thus attained an air of respectability, the flood-gates opened, and numerous studies were reported in the years which followed. This literature is extensively reviewed by GERNEZ-RIEUX, WAREMBOURG and PAUCHANT [1958]. Earlier, CANETTI [1955] had urged that controlled trials should be carried out in

pulmonary lesions, though he warned that such trials might be fraught with uncertainty and might finally have more disadvantages. A number of well-designed trials have been carried out subsequently, and these will be reviewed in the appropriate section.

In the pages which follow the author has endeavoured to evaluate the evidence warranting the use of corticosteroids in tuberculosis. After a brief review of the experimental and pathological background to the problem, the use of hormonal therapy is discussed in the various forms of the disease and the choice of drug and the associated risks briefly outlined.

Pathology: Experimental Tuberculosis

Before proceeding to examine the problem of the use of corticosteroids in humans, it is necessary to review briefly the evidence which is available from the studies carried out in experimental animals.

Lurie and Zappasodi [1955] describe the pathological changes thus: "Cortisone markedly increases the number of primary tubercles in the rabbit by inhalation of human type bacilli. However, these foci are small with little granulation tissue about the incompletely caseous pneumonic foci which swarm with bacilli. Yet the draining nodes contain few microorganisms. Typical tuberculous granulation with well developed caseation and marked lymphogenous dissemination occur in the controls.... The disturbed hormone balance produced by cortisone deprives many of the phagocytes of their innate capacity to inhibit the growth of the bacilli in their cytoplasm though their phagocytosis is not impaired. The interference with the destruction of the intracellular bacteria is paralleled by a retardation of the maturation of epithelioid cells in the hormone-treated rabbits.

"Cortisone reduces the fragility of capillaries and protects them against agents which increase the permeability of their walls. It does not protect the cells against cytotoxic allergic agents *in vitro*, yet the inflammatory response to tuberculin is markedly reduced *in vivo*. Cortisone so changes the ground substance that a barrier is interposed between the injured cells and the circulation.... The genetic resistance to tuberculosis may be controlled by the hormone balance." Stress is laid upon the fact that the most important aspect of resistance to tuberculosis is the capacity of the macrophages of the host to digest tubercle bacilli. Under the influence of large doses of cortisone, these cells, whilst retaining their ability to *ingest* the bacilli, lose their capacity to *digest* and destroy

them. Parallel evidence in the human was reported by FORBES [1961] who described the histological features in a patient who died of non-reactive tuberculous septicaemia and staphylococcal septicaemia, having been treated with triamcinalone 16 mg daily. No anti-tuberculosis chemotherapy had been given. Macrophage cells and polymorphs in the lymph glands showed clumps of tubercle bacilli within them and macrophages in the rib marrow were packed with tubercle bacilli. Throughout the liver and spleen there were numerous small miliary foci of necrosis which were packed with bacilli mostly within macrophages. Epithelioid cells, giant cells and lymphocytes were generally absent from all the lesions. CANETTI [1956] considered that LURIE's work on macrophages might be a clue to the fact that the anti-bacillary activity of macrophages are sometimes effective and sometimes ineffective, this being a major problem in the natural history of tuberculous infection.

SPAIN [1953] commented that there was also a reduction in the number of fibroblasts and that granulation tissue formation was inhibited. This tissue appeared to be less compact and did not progress so rapidly to collagenization. He further commented that it appeared that a balance between the dose of cortisone and the virulence of the noxious agent probably determined the extent of the change in the acute inflammatory process. Furthermore, although treatment with corticosteroids may be rewarded with suppression of the inflammatory reaction and less tissue destruction, it is also accompanied by increase in the number of tubercle bacilli and poorer localization.

There is wide variation in the reported effects of corticosteroids in the experimental animal. The earlier literature on this subject is very well reviewed by JOHNSON and DAVEY [1954]. Although many of the reports demonstrated that adverse effects occurred both with corticotrophin and cortisone—even in some instances when anti-tuberculosis chemotherapy was administered as well (COSTE, PIERRE-BOURGEOIS, GALMICHE, VIC-DUPONT, MOLLON, NAHEL and BLATRIX [1951]; KARLSON and GAINER [1952])—some investigations showed that hormonal therapy was not necessarily accompanied by adverse effects (LEMAISTRE and TOMPSETT [1951]; BACOS and SMITH [1953]). Cortisone was shown to have a deleterious effect on tuberculosis by SPAIN and MOLOMUT [1950] who found more extensive disease in guineapigs; by MICHAEL, CUMMINGS and BLOOM [1950] who found diffuse lesions in albino-rats which subsequently died from the disease, though normally immune; HART and REES [1950] who found increased susceptibility in the mouse; and ROBSON and DIDCOCK [1956] who found rapid dissemination lead-

ing to death in mice given intra-corneal inoculation of tubercle bacilli. BUNN and DROBECK [1952] showed that similar effects were produced by corticotrophin in rabbits inoculated intra-corneally.

There is thus convincing evidence, in certain experiments at least, that cortisone and, to a lesser extent, corticotrophin adversely affect tuberculosis in the experimental animal. The wide variation of effects in the experimental animal are no doubt due to the diversity of dose, frequency and preparation of hormonal therapy used and also to species variation. Both these aspects are also relevant to the investigations carried out in human tuberculosis. As JOHNSON and DAVEY remark: "Humans are variable in resistance and may behave like the guineapig or like the albino-rat depending upon individual susceptibility to tubercle bacilli."

Tuberculin Sensitivity

Brief reference must also be made at this stage to the effect of corticosteroids on the tuberculin skin test. Once again there is a morass of conflicting evidence, for some studies suggest that corticosteroids depress the reaction to tuberculin (LEMAISTRE, TOMPSETT, MUSCHENHEIM and MOORE [1950]; COMDEN and NETZER [1951]; MEYER, KINSELL and PARSONS [1952]) whereas others suggest that no change occurs (GERNEZ-RIEUX, WAREMBOURG and PAUCHANT [1958]) and increased tuberculin reactions were observed by LEBACQ and TIRZMALIS [1954]. However, many of the reports are based on small numbers of experimental animals or patients and there is a wide variation in the dosage and nature of hormones used.

Of special interest therefore is the study reported by SALOMON and ANGEL [1961], particularly as their results confirmed in general a controlled trial in 62 patients by JOHNSON, TAYLOR, JENNE, MORRISSEY, LOEB and MACDONALD [1960] who demonstrated that the mean diameter of the tuberculin reaction was much reduced at 8 weeks in patients receiving 16 mg methylprednisolone daily, 38% showing induration of less than 5 mm. All patients were tuberculin positive again at 6 months. SALOMON and ANGEL investigated the tuberculin reaction in 30 controls and 33 patients who, in addition to chemotherapy, were given ACTH commencing with 80 i.u. daily, and gradually reduced to a maintenance daily dose of 30–40 i.u. The observer was aware of the treatment group. Tuberculin tests were performed pre-treatment, at 6 weeks, at 3 months (a week after cessation of ACTH) and at 6 months. The changes

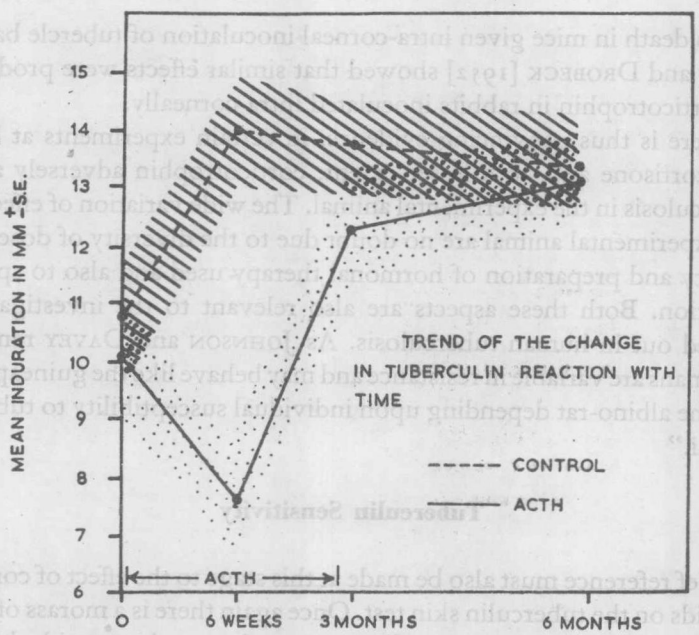

Fig. 1. The effect of adrenocorticotropic hormone (ACTH) on the tuberculin reaction. (Reproduced by permission of the Editor of the American Review of Respiratory Diseases.)

in the tuberculin reaction in each group is shown in fig. 1. At 6 weeks the mean induration in the ACTH group was reduced to almost half of that in the control group, a difference which is highly significant. At the end of ACTH treatment though the mean induration in the ACTH group was slightly lower than that in the controls the difference was not statistically significant. At 6 months there was no demonstrable difference between the two groups. Furthermore, whereas all 30 control patients increased the extent of the reaction at 6 weeks, only 5 of the 33 of the ACTH group did so, and one-third of the ACTH group became tuberculin negative. The behaviour of the tuberculin test in the control group (see fig. 1) was almost identical to that reported by ELLIS [1956] who studied serial tuberculin reactions in 100 patients with active chronic pulmonary tuberculosis.

SALOMON and ANGEL, discussing the implications of their findings, argue that one of them might be the increasing use of corticosteroids in the treatment of advanced toxic tuberculosis, the mechanism whereby toxicity is so well-controlled possibly being a suppression of a continuous endogenous tuberculin reaction. Of further interest is the in-

vestigation conducted by LANE, CLARKE and HOLMES [1956] who demonstrated that adrenocortical hyperfunction tended to be associated with a negative tuberculin reaction to the P.P.D. used in their study. In 48 patients—43 with tuberculosis and 5 non-tuberculous—the tuberculin reaction to a low dose of P.P.D. was related to the excretion of 17-ketosteroids. They observed that in 11 subjects who were negative to this strength of tuberculin the mean daily excretion of 17-ketosteroids was 16.3 mg compared to 8.2 mg in 37 patients who showed a positive reaction. This is a statistically significant difference. Furthermore, of 9 patients who excreted more than 15 mg of 17-ketosteroids per day, 8 were negative reactors. They concluded that endogenous adrenal hormones may influence the phenomenon of hypersensitivity in tuberculosis. The investigation reported by CITRON and SCADDING [1957] is also relevant as they showed that in active pulmonary tuberculosis the action of cortisone upon the size of tuberculin reactions was variable. In subjects showing a high degree of tuberculin sensitivity, reactions were reduced in size or inhibited; but the inhibiting effect diminished progressively with diminishing tuberculin sensitivity, until in subjects of low sensitivity the size of reactions produced by 100 T.U. was unchanged. In healthy tuberculin-insensitive subjects tuberculin plus cortisone caused no reaction. On the other hand, TRUELOVE [1957] studying 24 patients who were elderly and who showed frank signs of suprarenal cortical suppression associated with various diseases showed that small or moderate doses of corticosteroids restored the tuberculin reaction from negative to positive in 20 of them. He suggested that low dosages of corticosteroids are able to restore a tuberculin reaction which is suppressed by age, infection or suprarenal deficiency.

Adrenocortical Function in Tuberculosis

It has been established for some years that adrenocortical function is frequently depressed according to the severity of tuberculous disease both in humans and the experimental animal (RIVOIRE, JONNESCO and PASZKOWSKI [1950]; BASTENIE and KOWALEWSKI [1950]; BASSOLI and DE GIUSEPPE [1955]; CHAKRAVARTY [1963]).

A large detailed study carried out by CLARKE, ZAHN and HOLMES [1954] is illustrative of the pattern of adrenocortical function in this disease and the changes which take place in the course of treatment. These authors assessed adrenal function by the simplest single method of assessment at that time—neutral 17-ketosteroids expressed in mg/24

hours—in 109 patients, of whom 107 were considered to have active disease. Ninety-two suffered from pulmonary tuberculosis and 17 from other forms of the disease. They observed that the mean excretion was 8.93 ±4.78 mg per 24 hours in males and 8.61 ±2.65 mg per 24 hours in females. The absence of sex differences is interesting when it is recalled that the figure for males would normally be about one-third higher than that for females due to the secretion of androgenic substances from testicular tissue. The reduction in 17-ketosteroid excretion was significant even when the factor of age was taken into account. It was further observed that the 17-ketosteroid excretion was greatly reduced when frankly exudative disease was present in one or both lungs; was less reduced when exudative disease involved only part of one or both lungs; and above normal when disease was well-localised and "productive" in appearance. When the National Tuberculosis Association classification was applied to the results, 86% of patients with far advanced disease had excretion of an amount below normal, 37% of them showing an excretion of 50% or more below the normal figure; in 63% of patients with moderately advanced disease the reduction of excretion was less than 50% below normal; and 79% of patients with minimal disease had figures above normal values.

"Gratifying improvement" in the course of treatment occurred in those whose excretion of 17-ketosteroids rose to or had initially been near normal values; where improvement was slow or indefinite, the values remained at some distance above or below normal; and where the patient's condition worsened or death occurred, the value for excretion of 17-ketosteroids decreased. Nevertheless, examination of the adrenal glands of 4 of these subjects at autopsy showed no structural change.

The authors remark on the fact that one-third of the patients studied showed excretion values which were normal or high and demonstrated that emotional factors also seemed to play a part in the rate of excretion of 17-ketosteroids.

Another detailed study was carried out in Japan on 34 patients, estimating the total excretion of corticosteroids—unconjugated and conjugated 17-hydroxycorticosteroids and formaldehydogenic corticosteroids (UETE [1962]). The author demonstrated a significant correlation between the excretion of total corticosteroids and the severity of pulmonary tuberculosis. Low values were frequently seen in moderately or far advanced disease, largely due to reduction in the conjugated fraction. Some patients with far advanced disease had a decrease in the value of the unconjugated fraction as well. The good response to ACTH in these

patients suggested that the adrenal hypofunction was secondary in character. An improvement to normal values was observed on treatment with chemotherapy.

One further observation which may be of some importance is that a low concentration of serum sodium has been observed in chronic pulmonary tuberculosis, and in this connection it is of interest that a "biochemical death" is reported in tuberculous meningitis (LORBER [1960]). This aspect has been observed by several authors (THORN, HOWARD and DAYMAN [1940]; KOLMER, ELLIS, SMITH, COLLINS and GREISHEIMER [1948]). SHUSTER [1957] studied 40 patients with advanced active chronic tuberculosis with a poor prognosis and in whom hypotension, hyponatraemia and hyperpigmentation were frequently found. They observed that despite the hyponatraemia, sodium output remained appreciable, and that there was a normal plasma concentration of urea and potassium. Some patients had a low total output of corticosteroids and reduced water-load excretion. After administration of ACTH in a dosage of 80 i.u. of the gel or of long-acting ACTH, steroid output was increased, as was the water-load excretion, and there was a depression of the eosinophil count. They suggest that their findings are consistent with hypopituitarism. However, they admit that the general clinical findings did not suggest such a diagnosis and tentatively proposed that the abnormalities were attributable to a selective ACTH deficiency. The author refers to unpublished work in which improvement in pulmonary lesions in chronic advanced tuberculosis has been observed with a dosage as low at 10–15 i.u. of ACTH.

The complexity of the problem of adrenocortical function in tuberculosis may be reflected in the divergence of results which have been obtained in the corticosteroid treatment of patients who seem moribund at the time of commencement of treatment. Support for the effectiveness of corticosteroid therapy in such circumstances is given by a number of authors including BARRE, DANRIGAL and RICHIER [1955]; ELSBACH and EDSALL [1957]; HORTON, TRAVIS, LARKIN and PHILLIPS [1958] and DES PREZ and ORGANICK [1958]. However, the CO-OPERATIVE STUDY GROUP [1963] claimed that the use of hydrocortisone and cortisone in patients with severe infections, 17 of whom had tuberculosis, did not confer an advantage which was statistically significant in terms of survival. However, in this series corticosteroids appear to have been given for only 6 days. There are, furthermore, two controlled series in which opposite conclusions are reached (ALEMQUER [1955]; SIMPSON and MCCLEMENT [1964]). ALEMQUER [1955] studied 33 patients who were

Table I. Death prior to 30 days: Time between admission and death (after ALEMQUER [1955].

Group	No. of patients	Time between admission and death (days)			No. of deaths
		½–3	4–15	16–30	
Cortisone . . .	14	1	1	0	2 (14%)
Control	13	1	4	4	9 (69%)

suffering from advanced pulmonary tuberculosis and who were thought likely to be in danger of imminent death. These patients were allocated at random to a control series receiving chemotherapy only, and a treatment group who received cortisone parenterally in the following dosage:—300 mg from 1st to 3rd day, 200 mg 4th to 6th day, 100 mg 7th to 9th day, and 50 mg from 10th to 15th day. Six patients died within 12 hours—2 in the control group and 4 in the cortisone-treated group, but 2 of the latter died in fact before any cortisone was administered. The results obtained in the patients remaining in the two groups are shown in tables I and II. It will be seen that only 2 out of 14 (14%) of the patients treated with cortisone died within the first thirty days compared to 9 out of 13 (69%) in the control group. The favourable results obtained in the cortisone-treated group are statistically significant compared with the control group.

On the other hand SIMPSON and MCCLEMENT [1964] failed to find any significant difference in two groups of similar nature. Of 39 patients, 21 were treated with chemotherapy only and 18 received corticosteroids in addition in the form of 250 mg hydrocortisone on the first day, 60 mg of prednisolone on the 2nd and 3rd days and 40 mg daily subsequently and until such time as it was apparent that the patient's condition was satisfactorily maintained. Though precise details are not given, it is stated that neither group had gross disturbance of the serum electrolyte

Table II. Death related to extent of lesions (after ALEMQUER [1955])

Group		Volume of aerated lung compared to total lung volume (per cent)		
		15–30	31–50	51–95
Death	Cortisone . . .	67% (2/3)	0% (0/5)	0% (0/6)
	Control	100% (4/4)	67% (2/3)	50% (3/6)

levels but minor degrees of hyponatraemia and hypochloraemia were present in some patients, the incidence in the control group being twice that in the treatment group. It is further stated that in none had previous treatment with chemotherapy been given. Full resuscitative treatment, including intravenous medication, blood transfusion, tracheostomy and artificial respiration, was given when necessary. The results are given in table III. As will be seen, 57% of the control group and 45% of the corticosteroid group died in the first 14 days. It will also be observed that 10 patients died in the first 10 days in the control group (45%) compared to only 5 (28%) in the corticosteroid group. SIMPSON and MCCLEMENT [1964] comment that the series reported by ALEMQUER [1955] contained a number of patients who had previously received prolonged chemotherapy and that there was a wider range of pulmonary tissue involvement in this series. These differences ought to even themselves out in a controlled trial, though it would be important to know whether this was so. On the other hand, although treatment had not been given for more than a month in any of the New York series, there is no indication that the patients were analysed to see whether there was any difference in the percentage of drug-resistant organisms in the two groups of patients who presumably lived in a city which had a primary drug-resistance rate of 16.6% (CHAVES, DANGLER, ABELES, ROBINS and WIDELOCK [1961]). Furthermore, two-thirds of the New York series gave a definite history of alcoholism.

The question must therefore be posed as to whether—in view of the known fact that there is lowered adrenocortical function in severe tuberculosis and that there may also be significant biochemical changes—the difference lies in the fact that in one series cortisone was administered and in the other, prednisolone. It seems important to investigate this

Table III. Mortality and time of death in relation to admission to the study (after SIMPSON and MCCLEMENT [1963])

Interval between time of admission to study and time of death	Control Group (Total: 21)	Treatment Group (Total: 18)
24–48 hours	5	2
2–7 days	5	3
7–14 days	1	3
After 14 days	1	0
Total	12 (57%)	8 (45%)