CUTANEOUS MANIFESTATIONS OF TUBERCULOSIS IN THE WESTERN CAPE

A REVIEW OF THE LAST DECADE*

JEAN WALKER, M.B., CH.B. (CAPE TOWN)

Department of Dermatology, University of Cape Town and Groote Schuur Hospital

Skin tuberculosis has been chosen as the subject of this paper for two main reasons—firstly because a fair number of cases of one form or another is seen at the Cape, and secondly because the treatment of tuberculosis has undergone a revolutionary change in the last 10 years. The time therefore seems opportune for a general review of the situation.

For the 10-year period ended 31 May 1955 records are available at the Groote Schuur Hospital of 50 cases of tuberculoderms; of these, 34 are lupus, 6 scrofuloderma, 2 tuberculosis verrucosa cutis, 3 papulonecrotic tuberculid, 2 erythema induratum of Bazin, 2 rosacea-like tuberculid of Lewandowsky and 1 lupus miliaris disseminatus faciei. There have been no primary cutaneous complexes; these are rarely diagnosed in South Africa.[1]

As regards erythema nodosum, many cases are seen in dermatological, medical and paediatric out-patient sessions, but few are admitted. Unfortunately, records are obtainable only of warded cases; of these, there have recently been 4 patients suffering from tuberculosis who have presented with erythema nodosum, all of them children with demonstrable primary lung complexes.

It is remarkable that, amongst all the cases of florid, active pulmonary tuberculosis seen in their hundreds at the Cape institutions, the medical officers seldom see an eruption directly attributable to infection of the skin by the tubercle bacillus. Cipollaro[2] notes a similar state of affairs in the United States.

In the last 10 years 20,133 cases of tuberculosis have been notified to the Medical Officer of Health in Cape Town. Presumably, most cases of skin tuberculosis are seen at the Groote Schuur Hospital, rather than at the tuberculosis clinics and sanitoria, so that our figures are fairly representative of the total number of skin cases seeking advice.

The distribution of the 50 cases at the hospital was as follows: Cape Town (30), Strand (2), Kraaifontein (1), Philadelphia (1), Worcester (1), Genadendal (2), Bredasdorp (2), Tulbagh (1), Moorreesburg (1), Citrusdal (2), Van Rhynsdorp (1), Blanco (1), George (1), Prince Albert (1), Richmond (1), Port Elizabeth (1), Transkei (1). Most of the local patients live in the poorer parts of the Cape Peninsula and its environs.

It will be seen from these figures that tuberculosis of the skin is a relatively uncommon form in the Western Cape and is by no means the problem that it still remains in European countries,[3] despite the very high incidence of tuberculosis in general in South Africa. Perhaps the greater amount of sunlight is a factor in protecting the skin from invasion by the tubercle bacillus. Nevertheless, it is a problem that has to be tackled, particularly amongst the non-European lower income groups. Tuberculoderms are rare in European South Africans, only 5 cases having been seen at the Groote Schuur Hospital in the last decade, 3 of lupus and 2 of rosacea-like tuberculid. The figures and distribution of our cases are indicative of the important part played by bad socio-economic conditions in the etiology of cutaneous tuberculosis.

An attempt is being made to investigate the family backgrounds of all our cases; so far, very few have revealed tuberculosis in other members of the families.

The diagnosis of many of our cases has been confirmed by biopsies at the outset, and 'test of cure' biopsies are performed towards the end of the course of treatment. Acid-fast bacilli are very rarely seen in our histological sections. Tuberculin tests, erythocyte sedimentation rates and chest X-rays have been done as a routine measure in the last few years. Only 9 of the tuberculoderms were associated with active pulmonary tuberculosis (3 lupus, 2 erythema induratum, 2 scrofuloderma, 1 papulo-necrotic tuberculid and 1 tuberculosis verrucosa cutis). Five other cases showed calcified hilar glands. Of the 28 cases who were tuberculin tested, only 3 were negative; 1 was a Native boy with lupus and the other 2 were adult Europeans, the one a woman suffering from a rosacea-like tuberculid and the other a man with lupus-like lesions on the thigh, histologically found to be tuberculous. Of the 29 cases in whom an erythrocyte sedimentation rate was done, it was found to be raised in 18, of whom 6 had active pulmonary tuberculosis. It has been noted that the purely cutaneous cases usually show a gradual decline of the erythrocyte sedimentation rate towards normal as the lesions respond to treatment.

THE TREATMENT OF TUBERCULOSIS OF THE SKIN

Now that there are 4 powerful anti-tuberculous chemotherapeutic agents—calciferol, streptomycin, isonicotinic acid hydrazide and para-aminosalicylic acid—cutaneous tuberculosis can be regarded as curable in a reasonable period of time. This is a far cry from the sad old days when an adolescent with lupus would be doomed to a *via dolorosa* of clinics and unsatisfactory treatment, with gradual progression of the scarring, destructive process. Perhaps this is an exaggeration, because good results *were* obtained in a proportion of cases. Before the new era of treatment of lupus in the early nineteen forties, therapy aimed at improving the general condition and building up the body's resistance to infection by means of good food with supplementary vitamins, iron and general ultra-violet light baths. Even today we should continue to employ these general

*A paper presented at the South African Medical Congress, Pretoria, October 1955.

supportive measures, because we are, after all, dealing with a tuberculous state. Certain systemic modalities were used with varying success; for example, gold injections, thyroid extract, and tuberculin, which produced a marked local reaction in the lupus. Local destructive measures were frequently used, amongst which were surgical excision (which still has a place in very early lupus), scraping, arsenic, trichloracetic acid, salicylic acid, mercury, potassium permanganate, nascent iodine, lactic acid, acid nitrate of mercury, phenylethyl hydnocarpate and pyrogallic acid (in fact, the old story of the number of suggested remedies being almost directly proportional to the incurability of the disease in question). X-ray therapy was used at one time but fell into great disrepute because of the danger of malignant changes at the site; these, of course, can occur spontaneously in untreated lupus and, whereas epithelioma is the usual complication, the one case in our series which underwent degeneration developed a basal-cell carcinoma which had to be widely excised; she had had no radiotherapy to the lupus but had had years of ultra-violet light locally. Rodent ulcers are exceedingly rare in the pigmented races in this country, and it is possible that the prolonged, intensive exposure to actinic light might have been a factor in producing the basal-cell carcinoma in this Coloured woman.

Niels R. Finsen's name will forever be associated with the early cures of the hitherto incurable lupus. It was in 1895 that he first used his famous arc lamp in the treatment of lupus. A marked inflammatory reaction in the lupus was aimed at, to bring about destruction of the 'apple jelly' nodules, but only recently was it realized that the local formation of vitamin D in the tissues was probably partly responsible for the good results.

As Michelson says in his foreword to Riehl and Köpf's book: 'The therapy of lupus vulgaris was essentially a physical one until recent times when now the attack is largely chemical.[4]

Calciferol.

In 1943-4, Charpy in France published his excellent results of vitamin D2 in the treatment of lupus.[5-7] At about the same time, though independently, Fanielle in Belgium[8] and Dowling and Prosser Thomas in England[9-11] were using calciferol in large doses. This was an epoch-making step forward in the therapy of cutaneous tuberculosis. Calciferol has no action on the tubercle bacillus *in vitro* and is thought to act only on the tissues, stimulating connective-tissue proliferation and causing disintegration of the granulomatous deposits.[12]

Vitamin D2 is formed by the irradiation of its precursor, ergosterol, by ultra-violet light.[13] It has profound effect on calcium-phosphorus metabolism, influencing the absorption of calcium by reason of its action on the intestinal mucosa. In the treatment of cutaneous tuberculosis, calciferol is given in massive doses ranging from 50,000 to 300,000 international units a day. It is made up in tablet form, each tablet consisting of 50,000 units. The effective therapeutic dose approaches the limit of tolerance. Over-dosage produces hypercalcaemia, although symptoms may appear without any rise in serum calcium. There is, too, a rise in serum inorganic-phosphorus and blood urea, and a fall in plasma phosphatase. The marked withdrawal of calcium from the skeleton causes an increased urinary output of calcium and may eventually lead to osteitis fibrosa cystica and metastatic calcification in the soft tissues.

The earliest toxic symptom is, paradoxically, an unusual feeling of increased well-being which is, however, soon followed by anorexia, nausea, vomiting, headache, thirst, lassitude, muscular atony, constipation or diarrhoea with bloody stools, acute abdominal pain, psychic depression, polyuria with albuminuria and rapid loss of weight. An excess of calcium and phosphorus in the diet sensitizes the patient to intoxication by vitamin D; it is therefore inadvisable to supplement the calcium and phosphorus intake. Vitamin D is slowly excreted and has an accumulative effect; the toxic symptoms are, however, reversible on discontinuing the drug, although evidence of renal damage may persist for a year or more after cessation of treatment, particularly in adults. The erythrocyte sedimentation rate rises with approaching toxicity.

With these toxic effects in mind, there are certain routine tests which are regularly performed on patients on prolonged courses of calciferol, the most important of which are weekly estimations of serum calcium, inorganic phosphorus and urea, together with examinations of the urine for albumin and excess calcium. The patient must be weighed once a week and instructed to report immediately any of the symptoms just described. It is considered highly inadvisable to administer calciferol to patients suffering from active pulmonary tuberculosis. If metastatic calcification is suspected, straight X-rays of chest and abdomen will reveal this. If the serum-calcium level reaches 12 mg.% the dose of calciferol should be reduced or discontinued altogether. In view of the very toxic nature of this drug hospitalization of the patient for a few weeks or months is highly desirable.

Streptomycin.

This antibiotic is derived from the Streptomyces sub-group of the soil Actinomycetes. It first appeared in 1944 and has proved itself to be of inestimable value in the treatment of all forms of tuberculosis. In 1947 streptomycin was given, in combination with promizole, by O'Leary and others[14] to 15 cases of skin tuberculosis without any great success. In 1948 it was first used by Cornbleet[15] in combination with calciferol in the treatment of lupus vulgaris and was thought to enhance the effect of the latter in a synergistic way; Cornbleet suggested that calciferol sensitized the tubercle bacillus to the action of streptomycin. Charpy, Dowling and Prosser Thomas all observed residual nodules after prolonged treatment with vitamin D2. Cornbleet found that, after a 6-9 weeks' course of combined streptomycin and calciferol, the scars were thin and atrophic and contained no active nodules.

There are two forms of this antibiotic, dihydrostreptomycin and streptomycin; the former may have a permanent deleterious effect on the auditory nerve and the latter may damage the vestibule. It has been found that a combination of the two in equal parts is far less toxic than either used alone. They are bacteriostatic, not bac-

tericidal, and the tubercle bacillus soon develops resistance to them if they are used alone. In dermatological practice, the combination of dihydrostreptomycin and streptomycin is used, invariably in conjunction with calciferol, isoniazid or para-aminosalicylic acid.

As with all the other antibiotics, toxi-allergic eruptions are sometimes seen, usually of the erytheme multiforme or urticarial types, but occasionally morbilliform, scarlatiniform or haemorrhagic. True exfoliative dermatitis has been known to supervene. Most of these eruptions appear within the first 10 days of treatment and are easily controlled by antihistaminics. Stomatitis and generalized pruritus may be distressing symptoms. The most serious side-effects of these two antibiotics are those resulting from damage to the auditory nerve and vestibule, leading to deafness, tinnitus and vertigo. Permanent deafness as a rule only results from intrathecal use of dihydrostreptomycin for tuberculous meningitis,[16] but has recently been described after prolonged intramuscular use.

Isonicotinic Acid Hydrazide (Isoniazid, INH)

This drug made its appearance early in 1952. It is a coal-tar compound and is not really a newcomer, its formula having been discovered in Prague 40 years ago. It was discarded and forgotten until, in 1945, a French scientist observed that niacinamide, in the vitamin-B constellation, inhibited the growth of the tubercle bacillus in animals. Chemists of the Squibb and Hoffman-La Roche laboratories, working independently, after 5 years' research isolated isonicotinic acid hydrazide which could be cheaply produced and was effective, when taken by mouth, in inhibiting the *Mycobacterium tuberculosis*. It is well known that *in vitro* the bovine bacillus is insensitive to INH whereas, in actual practice, lesions produced by these organisms respond very well; this would seem to be an indication of the unreliability of laboratory procedures when attempting to assay the antibacterial efficacy of a drug.[17] Unfortunately, *in vivo* the organism does very soon become resistant to INH, but this can be combated by giving streptomycin or PAS at the same time.

Isoniazid is given by mouth in tablet form, each tablet consisting of 50 mg. The dose is 3-6 mg. per kg. of body-weight per day, the usual amount given to an adult being 200-400 mg. per day in 3 or 4 divided doses.

The toxic effects of INH simulate vitamin deficiencies and are largely the result of irritation of the central and automatic nervous sytems. Side-effects are rare, particularly in children, and tend to occur during the first 3 weeks of treatment; they usually disappear in spite of persistent administration of the drug. The symptoms referable to the nervous system consist of muscular twitchings, hyperreflexia, vertigo, dryness of the mouth, constipation, hypertonia of the bladder sphincter, euphoria, mental excitability and insomnia. Peripheral neuritis with marked sensory distubance has been described by Linton, Rabinowitz and Olie at Springkell[18] and by others elsewhere. Anorexia, loss of weight and jaundice due to toxic hepatitis are occasionally met with, and transient blood-changes in the form of eosinophilia and mild anaemia have been observed.

The vitamin-B group, particularly pyridoxine, is useful in counteracting many of the toxic effects of INH. It is thought that INH exerts an antivitamin effect by blocking the action of nicotinic acid and pyridoxine, or that it depletes the tissues of pyridoxine.[19] An acute pellagrinous picture has been described by McConnell and Cheetham.[20]

Para-aminosalicylic Acid (PAS)

This drug has only a very slight bacteriostatic effect on the tubercle bacillus but is of immense value in reducing the resistance of this organism to streptomycin and INH, and is now used almost exclusively as an adjunct to these latter in the treatment of tuberculosis It is given by mouth in tablet form, each tablet consisting of $\frac{1}{2}$ g. of PAS, in 4-hourly divided doses totalling 12-20 g. a day. Children are given 125 mg. per kg. of body-weight, in orange juice, 6-hourly.

PAS is apt to cause the same toxic symptoms as the other salicylates, namely, drug fever, rashes, tinnitus, nausea, vomiting, diarrhoea, jaundice and hypokalaemia with paralyses and cardiac arrhythmias. Lymphadenopathy, hypoprothrombinaemia, albuminuria, haematuria and even anuria have all been reported. It should be mentioned, in passing, that PAS reduces Benedict's reagent; this is obviously of importance when treating patients who are suffering from diabetes as well as tuberculosis.

EXPERIENCES AT THE GROOTE SCHUUR HOSPITAL

In 1944 we first used calciferol for lupus vulgaris at Groote Schuur Hospital. Nine years ago, I read a paper at the Durban Congress giving our results in the few cases we had treated. We were very pleasantly surprised by the comparatively good outcome, although it was still a matter of half a year or more before any striking improvement took place (Figs. 1 and 2).

In 1949 we first combined streptomycin with calciferol

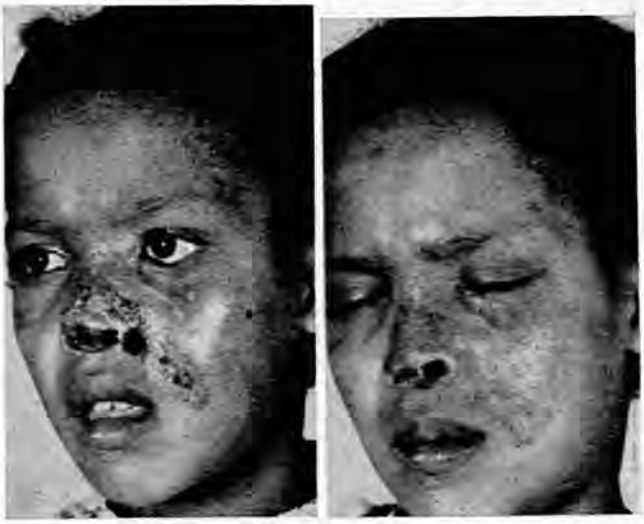

Fig. 1. Fig. 2.

Fig. 1. The first case treated with calciferol at Groote Schuur Hospital. Before treatment.
Fig. 2. Same case as Fig. 1 after 5 months on calciferol.

and were even more gratified by the distinctly quicker progress of our cases.

In 1952 we decided to try out the new isonicotinic acid hydrazide. We used it alone at first and were astounded by the remarkably rapid healing of a very severe case of scrofuloderma within 3 weeks (Figs. 3 and 4).

Since then we have used varying combinations of INH, streptomycin and PAS with, on the whole, very satisfactory results in most cases, although some seem to become resistant to these 3 after a while; under these circumstances, we use calciferol, which invariably has the effect of finally clearing up the skin infection.

Table I gives more detailed information about the 4 drugs.

We have formed certain general impressions about the chemotherapy of the tuberculoderms.

The earlier cases on INH cleared with astonishing rapidity, so much so that we found ourselves saying that INH could do in weeks what it took calciferol months to accomplish. We have, however, had to revise that opinion in the last 2 years, and it seems as though the tubercle bacillus has become fairly resistant to this newest and most dramatic of the chemo-therapeutic agents at our disposal, a situation perhaps comparable with the resistance to penicillin that has been acquired by the staphylococcus. We, therefore, remain loyal to calciferol, which is still the great stand-by when INH, streptomycin and PAS let us down.

The true tuberculous infections, lupus and scrofuloderma, tend to respond better to chemotherapy than do the so-called tuberculids, particularly the more anergic forms like lupus miliaris disseminatus faciei. Michelson[21] states that it has been the experience of the German dermatologists that lupus miliaris does not respond to INH, somewhat strengthening the view that, in spite of its histology, it may not be tuberculous. Our case showed very little improvement while on INH and streptomycin, but healed on calciferol.

At this point, sarcoid might be mentioned. This is not the time to go into the whole vexed question of sarcoidosis, but one might just say, in passing, that two cases of nodular sarcoid cleared up on calciferol without any of the unpleasant sequelae so often manifested in this disease.

We have been most fortunate in the rarity of side-effects and symptoms of toxicity in our patients. Ten of our 50 cases exhibited side-effects to calciferol and 2 of these 10 to streptomycin as well. The calciferol intolerance revealed itself as hypercalcaemia, excess urinary calcium, albuminuria, dryness of the mouth with fatigue, nausea and anorexia, acute abdominal pain, constipation and headaches. One patient who showed signs of intolerance to streptomycin complained of clicking and deafness in the ears and the other had an anaphylactic crisis. They all recovered within a few days of discontinuing the drugs and, in some instances, were able to tolerate later courses very well.

Local ultra-violet light therapy is given throughout the course of chemotherapy.

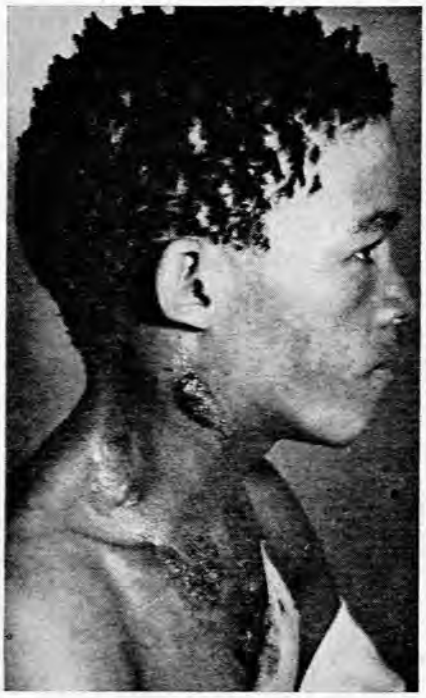

Fig. 3.

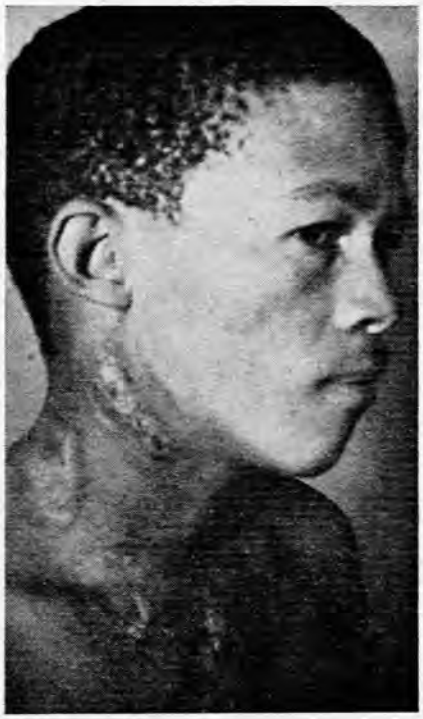

Fig. 4.

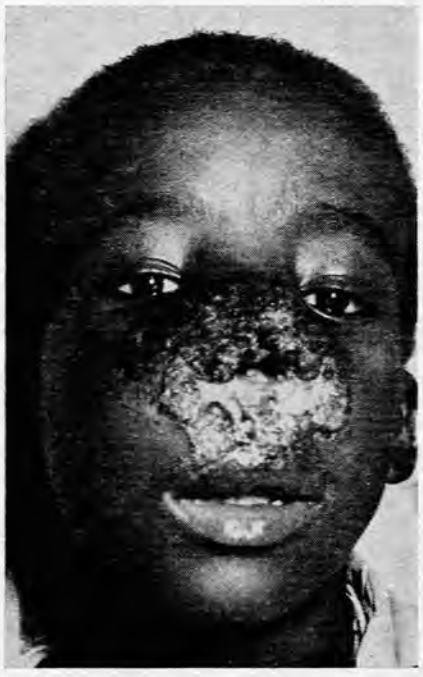

Fig. 5.

Fig. 3. The first case treated with INH at Groote Schuur Hospital. Before treatment.
Fig. 4. Same case as Fig. 3 after 3 weeks on INH.
Fig. 5. Neglected lupus.

The great advances in plastic surgery have made possible the repair of ravaged faces, now that dermatologists are able to eradicate the active tuberculous process before destruction of tissue has progressed too far. Before operating it is essential to wait, for at least 6 months after apparent cure, to be certain that no new lupus nodules are forming.

CONCLUSION

I can best summarize my talk by the remark that, nowadays, when a patient with lupus comes in, our former sense of frustration and commiseration has been replaced by a feeling of joy that yet another sufferer seeks easily-procured relief from one of the most distressing of maladies.

All forms of cutaneous tuberculosis are compulsorily notifiable in South Africa. Perhaps because of their non-infectious nature, this is not realized by all practitioners.

BCG vaccination is worthy of mention. It is not as yet being practised on any large scale at the Cape, but, when it is, we may expect to see the occasional case of lupus developing at the site of innoculation.[22-25]

I should like to have the news of the great efficacy of the modern therapy of lupus blazoned to all the corners of the Union of South Africa, so that the sufferings of the people in the locations and slums may be alleviated by this treatment, which is simple and may readily be carried out by the District Surgeons in collaboration with the District Nurses. Hospitalization is by no means essential when streptomycin, INH and PAS are used, and complicated laboratory procedures may well be dispensed with. Fig. 5 illustrates a tragedy that to-day is a disgrace in a civilized country.

I should like to thank Dr. N. H. G. Cloete, Superintendent of Groote Schuur Hospital, Cape Town, and Dr. R. Lang, Head of the Department of Dermatology, for permission to publish this paper. Thanks are due, too, to Mr. B. Todt for the photographs.

TABLE I

VITAMIN D2 (CALCIFEROL)

Tablets: 50,000 i.u. each. Oral.
Dose: 50,000 to 300,000 i.u. daily.
Contra-indications: Pulmonary tuberculosis, arteriosclerosis, kidney disease.
Toxicity counteracted by vitamin A (partly).
Toxic Effects mainly due to altered calcium-phosphorus metabolism.

Symptoms and Signs of Toxicity

Early increased feeling of well-being.
Anorexia, nausea, vomiting, constipation or bloody diarrhoea
Acute abdominal pain.
Pyrexia.
Rapid loss of weight.
Dry mouth, thirst.
Polyuria, albuminuria, increased urinary Ca.
Hypertension.
Headache, psychic depression, hazy memory, dizziness, mandibular neuralgia, tender gums and teeth. Paraesthesia, peripheral neuritis, optic atrophy. Retinal vessels affected.
Muscular and articular pains.
Libido increased or diminished.
Leucocytosis. ESR rises with approaching toxicity.
Increased tuberculin allergy during treatment is a favourable sign.
Metastatic calcification (if in placenta, foetal death may occur).
Rarefaction of bones.
Increased serum calcium, inorganic phosphorus and blood urea.

STREPTOMYCIN

Intra-muscular injection.
Dose: 1 g. daily at first. Children: 0·01 g./kg body-weight/day.
Contra-indications: None, unless known allergic sensitivity is present.
Toxicity counteracted by antihistaminics (partly).
Toxic Effects: Allergic and aural.

Symptoms and Signs of Toxicity

Tinnitus, vertigo, deafness.
Eruptions: Urticarial, erythema multiforme, morbilliform, scarlatiniform, haemorrhagic, exfoliative dermatitis.
Stomatitis.
Pruritus.
Anaphylaxis.
Tight feeling around the mouth.
(Contact dermatitis in personnel).

ISONICOTINIC ACID HYDRAZIDE (INH)

Tablets: 50 or 100 mg. each. Oral.
Dose: 3-6 mg./kg body-weight, usually 300-400 mg. daily. Children: 6 mg./kg.
Contra-indications: None. Avoid concomitant administration of CNS stimulants (ephedrine, belladonna, adernaline).
Toxicity counteracted by: Pyridoxine.
Toxic Effects mainly due to stimulation of central and autonomic nervous systems.

Symptoms and Signs of Toxicity

Anorexia (or enormous appetite), dry mouth, heartburn, nausea, vomiting, constipation or diarrhoea, abdominal discomfort.
Loss of weight.
Jaundice.
Transient flushing of face.
Peripheral neuritis. Paraesthesia. Burning feet. Muscular twitching. Motor restlessness. Ataxia. Coarse tremors. Hyperreflexia. Transitory Babinski sign. Bladder sphincter hypertonia. Retention.
Transient albuminuria.
Vertigo. Euphoria. Insomnia. Mental excitability and irritability. Fatigue. Loss of memory. Meningism. Increased susceptibility to convulsions in epiletics. Confusional psychosis. Headache. Stupor. Drowsiness.
Hypotension. Palpitations. Angina in arterisclerotics.
Death in respiratory failure.
Anaemia. Eosinophilia. Increased coagulation time. Increased bleeding tendencies. Agranulocytosis.
Eruptions: Eczematous. Generalized desquamation. Herpes zoster.
Pellagra.
(Contact dermatitis in personnel.)

PARA-AMINOSALICYLIC ACID (PAS)

Tablets: ½ g. each. Oral.
Dose: Adults 12-20 g. daily. Children ½ g./kg. daily in orange juice.
Contra-indications: None.
Toxicity counteracted by: Sod. bicarb. for gastric-intestinal disturbances.
Toxic Effects similar to other salicylates.

Symptoms and Signs of Toxicity

Rashes.
Drug fever.
Nausea, vomiting, diarrhoea.
Jaundice.
Lymphadenopathy.
Hypokalaemia.
Cardiac arrhythmias.
Hypoprothrombinaemia.
Tinnitus.
Albuminuria. Haematuria. Anuria. Urine (reduces Benedict's).

REFERENCES

1. Chitters, M. (1949): S. Afr. Med. J., **23,** 103.
2. Cipollaro, A. C. (1944): N.Y. St. J. Med., **44,** 1557.
3. Aitken, R. (1946): *The Problem of Lupus Vulgaris.* Edinburgh: E. & S. Livingstone.

4. Riehl, G. and Köpf, O. (1955): *The Therapy of Skin Tuberculosis*. Illinois: C. C. Thomas.
5. Charpy, M. J. (1943): Ann. Derm. Syph., **3**, 331.
6. Charpy, M. J. (1944): *Ibid.*, **4**, 110.
7. Charpy, M. J. (1948): Brit. J. Derm., **60**, 121.
8. Fanielle, M. G. (1942): Scalpel, **95**, 539.
9. Dowling, G. B. and Prosser Thomas, F. W. (1945): Proc. Roy. Soc. Med., **39**, 96.
10. *Idem.* (1946): Lancet, **1**, 919.
11. Dowling, G. B. (1948): Brit. J. Derm., **60**, 127.
12. Goldsmith, W. N. and Heller, F. F. (1954): *Recent Advances in Dermatology*, 2nd ed., p. 217. London: J. & A. Churchill.
13. Reed, C. I., Struck, H. C. and Steck, I. E. (1939): *Vitamin D: Its Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigation*. University of Chicago Press.
14. O'Leary, P. A., Ceder, E. T., Hinshaw, H. C. and Feldman, W. H. (1947): Arch. Derm. Syph., **55**, 222.
15. Cornbleet, T. (1948): J. Amer. Med. Assoc., **138**, 1150.
16. British Pharmaceutical Codex (1954).
17. Sulzberger, M. B. and Baer, R. L. (1954-5): *Yearbook of Dermatology and Syphilology*, p. 96. Year Book Publishers. Quoted from Marchionini, A., Spier, H. W. and Rockl, H. (1953): Hautarzt, **4**, 497.
18. Linton, W. S., Rabinowitz, E. and Olie, M. (1952): S. Afr. Med. J., **26**, 889.
19. Annotation (1955): Brit. Med. J., **1**, 1203.
20. McConnell, R. B. and Cheetham, H. D. (1952): Lancet, **2**, 959.
21. Michelson, H. E. (1955): Arch. Derm. Syph., **71**, 664.
22. Marcussen, P. V. (1954): Brit. J. Derm., **66**, 121.
23. Foreign Letter from Norway (1954): J. Amer. Med. Assoc., **155**, 61.
24. Annotation (1954): Brit. Med. J., **2**, 1095.
25. Editorial (1955): Brit. Med. J., **1**, 1076.