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EDITORIAL

On pages 29-37 we have abstracted as fully as space permits a book called *Experimental Tuberculosis, Bacillus and Host, with an Addendum on Leprosy*. It includes 25 papers (along with discussions) which were read at a symposium called by the Ciba Foundation in October, 1954. The papers may be roughly divided according as they deal with the tubercle and leprosy bacillus, or with the monocyte or phagocytic cell which seeks to destroy the bacillus. For, though other factors come into the picture, the real issue is the struggle between the bacillus and the cell which engulfs it. This cell, depending on its condition at the time, either grants the bacillus sanctuary and facilities for multiplication, or else destroys it. This dual bacillus-cell relationship, common to both diseases, is described by Lowe(2)* as " a curious dichotomy," and by Lurie(1) as symbiotic and nodular phases.

Taking the bacillus first, as being the aggressor, its composition is studied under proteins (5), lipids (8, 15), and polysaccharides(7, 8). While proteins are used in *testing* sensitivity to the tubercle bacillus, polysaccharides associated with lipids are becoming increasingly regarded as responsible for *causing* skin and cellular reactions and immunity generally(8, 15). Mycolic acids(6) (lipopolysaccharides) have been found to vary in their composition according to the virulence of tubercle bacilli. Mycolic acids are also supposed to be indirectly responsible for the acid-fastness of mycobacteria by participating in the formation of an impermeable surrounding film; and thus virulent mycobacteria are stained red with neutral red and avirulent stains yellow.

Virulence is also discussed in connection with the cord factor(12), which is partly responsible for virulence, and when injected in infected mice can cause a flare up and rapidly progressive disease.

Several papers deal with the important period when infection first takes place. When many bacilli are inoculated into an animal there is a discrepancy between the wide-spread lesions and the few acid-fast bacilli that can be detected. Is it possible that there is a granular or nonacid-fast cycle in the life of mycobacteria?(19). This is an important question which has often been raised in connection with *Myco. leprae*. The role of early tissue reactions in determining whether the host or the bacillus will win

* The numbers in the text correspond with the numbers of the abstracts on pages 29-37.

is shown by the use of adrenalin or "Liquoid"[10], which act as temporary inhibitors of defence reactions. The importance not only of response to infection but of sufficiently rapid and early response is shown in Hanks' paper[4]. It may be that B.C.G.[20] furnishes just this little extra resistance to turn the tables between progressive and arrested infection. Hanks'[4] suggestion of mixing dead lepra bacilli with the living B.C.G. vaccine for increasing the possible protective power of the latter is worth following up.

It is questioned[13] whether the serological differences between the different antigenic constituents of culture filtrates of the tubercle bacillus are of any specific significance in relation to tuberculous disease. It is suggested[14] that the haemagglutination test indicates only an enhancement of a non-specfic reaction. In leprosy, in the lepromatous type with abundant bacilli, there are plenty of circulating antibodies but, as is shown by the lepromin test, there is no sensitization and no resistance to infection; while in the tuberculoid case, where these signs of resistance are found, antibodies in the blood are difficult to find[2].

If we pass from the bacillus to the phagocytic cell (monocyte or macrophage), what are the factors which determine resistance, or the symbiotic versus the nodular phase? Suter[17] shows by *in vitro* study that in tuberculosis after vaccination the growth-inhibitory power of monocytes is independent of hypersensitivity, although both of these appear at about the same time. He shows that hypersensitivity along with large numbers of bacilli in the cells seems to favour multiplication of bacilli; whereas if the bacilli are few, hypersensitivity allows full inhibitory power to the cells. Does this correspond to the well-known phenomenon in leprosy, where the acute exacerbation (lepra reaction) in the lepromatous type (where there are many bacilli) is followed by the disease getting worse, whereas in the acutely reacting tuberculoid (where there are few bacilli) the result is not infrequently a spontaneous clearing up of the lesions?

Various substances, such as fatty acids, have the power to produce the "nodular phase" with its follicular formation, epithelioid and giant cells, and caseation [9]. But comparatively large quantities are necessary as compared with the follicle-producing power of a single bacillus, be it that of tuberculosis or leprosy.

The effects of cortisone on the monocyte are instructive[21] in its power to inhibit multiplication of bacilli, though not to inhibit phagocytic power. To what extent is the type of leprosy influenced by the endocrine system?

The effect of INH[23] in producing metaplasia, destruction of bacilli, and epithelioid and giant cell formation, may be contrasted with the results of sulphone treatment in lepromatous leprosy. Does something of this nature occur when the border-line type heals up promptly under treatment?

The effect of surface-wetting agents[24] in experimental tuberculosis opens up new possibilities. Leprosy workers in search of more effective forms of treatment will watch with interest for further results.

* * * *

In the *British Medical Journal* (Nov. 5, 1955, p. 1106) certain substitutes for B.C.G. are mentioned. Among these is Salvioli's "V.D.S." diffusing vaccine which consists of a mixture of heat-killed human and bovine tubercle bacilli with hyaluronidase added to it. This has been used extensively in Italy where it is found that the hyaluronidase produces in the dead bacilli a migratory property characteristic of living organisms, and indeed produces lesions in the regional lymph nodes that are not seen when dead bacilli are used alone. It may be worth while testing this vaccine as to its power to turn a negative into a positive lepromin reaction. If it has this effect to the same degree as B.C.G., further tests would be called for to determine its possible use in the prophylaxis of leprosy. There would appear to be less risk with a dead than a living vaccine. Also there would be additional advantage in primitive field conditions, far from adequate laboratory facilities, where it is difficult to maintain living cultures.

Egypt. Annual Report for 1950.

This is just to hand. During the year 783 new patients with leprosy presented themselves, making a total of 12,484 recorded since leprosy control began in 1929. There are 974 patients in segregation in the Abu Zaabal (637) and Amira (284) colonies and in annexes to the five clinics. Hydnocarpus oil was still the main treatment, but a beginning was being made with "Sulfa compounds."

EXPERIENCE WITH "AVLOSULFON" SOLUBLE

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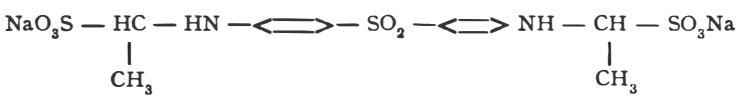
"Avlosulfon" Soluble is a preparation recently introduced for administration by injection in the treatment of leprosy. It consists of a 40 per cent W/W sterile aqueous solution of a disubstituted derivative of diaminodiphenyl sulphone known chemically as N:N'diethyl-4:4' diaminodiphenyl sulphone-a;a' disulphonate. This substance is freely soluble in water and breaks down rapidly in the body to release half its weight of DDS. Its molecular structure is as follows.



Laboratory investigations on the absorption and excretion of this substance were begun by the late Dr. Lowe at the Nigeria Leprosy Service Research Unit shortly before his retirement. The work was taken over while still in its infancy, expanded, and later supplemented by a clinical trial of limited proportions, the impressions gained from which are recorded here, together with the laboratory findings.

Estimations of sulphone in blood and urine were undertaken at intervals during the three days following the administration of "Avlosulfon" Soluble to volunteers in doses of ½ cc., 1 cc., and 2 cc., equivalent to 200 mg., 400 mg., and 800 mg. of the drug. For the purposes of comparison a second series of estimations was undertaken following the oral administration of DDS in doses of 100, 200, and 400 mg. under strictly comparable conditions. In each volunteer as long a series of estimations was undertaken as was practicable. The standard Bratton and Marshall method as modified by Brownlee was used. Estimations were made both of total sulphone and sulphone extractable by benzene. The very large number of estimations involved were undertaken by Miss F. McNulty, Mr. G. Okezie and Mr. S. Drewett. The results are given in Tables 1—4.

TABLE I

Blood concentration of sulphone after the administration of "Avlosulfon" Soluble.

Dose in mg.		*Average blood concentration in mg. per cent estimated as DDS At hours*							
		1	2	3	4	6	24	48	72
200	No. of estimations	4	13	10	3	6	9	6	4
	Total sulphone ...	0.475	0.45	0.45	0.42	0.26	0.15	0.14	0.1
	Extracted sulphone	0.26	0.22	0.17	0.19	0.1	0.1	0.06	0.05
400	No. of estimations	7	10	8	3	3	6	2	4
	Total sulphone ...	0.64	0.79	0.62	0.58	0.41	0.22	0.15	0.1
	Extracted sulphone	0.36	0.27	0.23	0.25	0.20	0.18	0.1	0.08
800	No. of estimations	13	13	13	3	3	20	20	20
	Total sulphone ...	1.43	1.20	1.04	0.80	0.62	0.28	0.18	0.11
	Extracted sulphone	0.30	0.34	0.28	0.33	0.28	0.17	0.125	0.095

TABLE II

Blood concentration of sulphone after the administration of DDS orally.

Dose in mg.		*Average blood concentration in mg. per cent At hours*							
		1	2	3	4	6	24	48	72
100	No. of estimations	5	5	4	5	5	5	5	5
	Total sulphone ...	0.22	0.27	0.30	0.35	0.34	0.21	0.17	0.16
	Extracted sulphone	0.11	0.13	0.145	0.145	0.14	0.1	<.1	<0.1
200	No. of estimations	9	9	9	9	8	9	9	7
	Total sulphone ...	0.38	0.59	0.72	0.73	0.67	0.35	0.24	0.14
	Extracted sulphone	0.16	0.28	0.34	0.345	0.29	0.19	0.10	0.05
400	No. of estimations	6	6	6	6	6	6	26	26
	Total sulphone ...	0.52	0.69	0.82	0.94	0.8	0.62	0.31	0.17
	Extracted sulphone	0.23	0.32	0.39	0.43	0.39	0.31	0.14	0.08

TABLE III

Urine concentration of sulphone after the administration of "Avlosulfon" Soluble.

Dose in mg.		*Average urine concentration in mg. per cent estimated as DDS At hours*								
		1	2	3	4	6	12	24	48	72
200	No. of estimations	8	2	3	3	5	3	5	6	
	Total sulphone ...	4.15	8.0	8.4	5.5	4.4	1.8	1.1	1.0	
	Extracted sulphone	3.4	4.8	4.9	2.5	1.9	0.9	0.15	0.16	
400	No. of estimations	7	3	6	3	3		6	3	7
	Total sulphone ...	4.2	5.2	8.8	7.5	4.5		1.8	1.1	0.15
	Extracted sulphone	1.7	2.4	4.4	3.2	2.1		0.4	0.3	0.06
800	No. of estimations	4	4	4	4	4	1	3	3	3
	Total sulphone ...	4.5	12.3	20.0	18.5	14.9	7.2	2.6	0.5	0.3
	Extracted sulphone	1.7	5.5	9.3	7.9	6.6	3.1	1.0	0.3	0.10

TABLE IV

Urine concentration of sulphone after the administration of DDS orally.

Dose in mg.		*Average urine concentration in mg. per cent At hours*								
		1	2	3	4	6	12	24	48	72
100	No. of estimations	5	5	4	4	5	1	5	5	5
	Total sulphone ...	0.4	0.5	0.6	0.6	0.75	1.0	1.1	2.4	1.2
	Extracted sulphone	0.1	0.1	0.14	0.22	0.26	0.3	0.37	0.71	0.4
200	No. of estimations	9	8	7	8	4	1	9	9	9
	Total sulphone ...	0.98	1.33	1.70	1.76	1.1	1.4	2.0	1.6	1.2
	Extracted sulphone	0.24	0.36	0.46	0.54	0.48	0.45	0.77	0.67	0.43
400	No. of estimations	6	6	6	6	6		6	6	6
	Total sulphone ...	1.6	2.2	3.3	3.8	4.2		4.2	2.6	2.0
	Extracted sulphone	0.70	0.97	1.4	1.8	1.9		1.8	1.2	0.9

Comments

1. THE CONCENTRATION OF TOTAL SULPHONE

The figures for total sulphone following the administration of DDS call for little comment. They are in line with previous records here and are similar to the published findings of other workers. On the whole in our Africans peak levels were rather lower and were attained more quickly than in Indian subjects (Dharmendra 1950b). Apart from this the general characteristics follow the now familiar pattern. The rapid absorption and slow excretion of DDS is evident, with peak blood levels at 4-6 hours after administration, followed by a slow decline, so that after 72 hours the concentration can still readily be estimated. In urine the peak concentration shows a considerable time lag as compared with blood, and declines even more slowly, so that after 72 hours the concentration is still relatively high. During the first 12 hours, with a dosage over 100 mg., not more than 10% of the dose administered has appeared in the urine.

With " Avlosulfon " Soluble the picture is different. At all doses tested the peak concentration of sulphone in the blood occurred within two hours of administration, but was considerably higher than that attained with the corresponding dose of DDS given orally. This high level is however evanescent, and rapidly declines, so that from about the sixth hour onwards the blood concentration falls below that attained with oral DDS in corresponding dosage. Thereafter it continues lower, and falls more rapidly, until after 72 hours the level is only about 0.1 mg.% regardless whether the dose administered was 200, 400 or 800 mg. The concentration of sulphone in the urine corresponds with these findings. Much

higher levels are attained than following oral DDS, and by 12 hours after administration approximately twice as much has already been excreting in the urine. These findings are in general agreement with those of Touzin and Merland. (Touzin and Merland 1953).

2. THE CONCENTRATION OF EXTRACTABLE SULPHONE

Extraction with benzene is a recognised method of estimating free DDS in mixtures with complex sulphones. It was discussed and applied by Lowe. (Lowe, 1952). During the course of the present work we have not found benzene an entirely satisfactory extractant. Nevertheless it appears to be selective in its action and results follow a consistent pattern both in respect to changes in dosage and to varying times. Where body fluids are concerned it also appears that more is involved than a simple matter of the relative solubility of DDS in water and in benzene. These matters are being considered further elsewhere. We are here concerned primarily not with the absolute concentration of DDS but with comparing the behaviour of "Avlosulfon" Soluble and DDS under corresponding conditions, and from that standpoint the results are interesting and instructive.

Following the administration of DDS, we were able to extract with benzene only 40-50% of the total sulphone present in blood. This proportion remained very constant from the first hour onwards, and did not vary with increase of dose, extractable sulphone thus bearing a constant relationship to the total amount of sulphone present regardless of the actual level of this. In urine, following a dose of 100 mg. DDS, the proportion of extractable sulphone was at first very low, less than 30% of the total, but increased up to a peak level after about 4 hours, following which it declined again. With higher doses the proportion of extractable sulphone tended to approximate more to that found in blood, but the actual levels of both total and extracted sulphone rose much higher than in blood. Taken together, these findings are not capable of explanation simply on the assumption that benzene fails to extract all the DDS present. This may be a fact, but some other factor is also operating. It has been suggested that after absorption DDS in part undergoes a chemical change whereby soluble products are constantly synthesised in small amounts. Our findings would not be inconsistent with this suggestion.

With " Avlosulfon " Soluble the discrepancy between total sulphone and that extractable by benzene is also very noticeable, both in blood and urine. If delay occurred in the body in the breakdown of " Avlosulfon " Soluble to DDS, such a discrepancy would be expected, and would be most marked at first, but tend to disappear with the passage of time. This effect is in fact seen in blood with a dose of 800 mg., but it is not seen with smaller doses, and the findings again suggest that a complex situation is present.

Where actual levels are concerned it is worthy of note that for an hour or so after administration, "Avlosulfon " Soluble yielded a little more extractable sulphone in the blood than did the corresponding dose of DDS This phase was, however, brief, and from the fourth hour onwards DDS continuously produced a higher figure.

" Avlosulfon " Soluble is thus absorbed into the blood more rapidly than DDS given orally, but it is also excreted much more rapidly than the parent compound. With larger doses there may be some delay in the breakdown of this substance to DDS, but in all the circumstances examined a considerable part of the sulphone present was in a form not capable of extraction by benzene, and suggested a complex situation in which free DDS was not the only breakdown product of " Avlosulfon " Soluble present.

It is of interest to observe whether the differences in behaviour between " Avlosulfon " Soluble and DDS have any bearing on the chemotherapeutic activity of the two substances.

CLINICAL TRIAL OF " AVLOSULFON " SOLUBLE

In examining the therapeutic activity of " Avlosulfon " Soluble we were not concerned to establish the fact of its activity against infection with M. Leprae. That could be assumed on the basis of its breakdown to DDS, incomplete though that may be. It was of greater interest to compare the speed of response to it with that expected from the use of oral DDS, in circumstances where its more widely fluctuating blood levels would be operative. It was also of interest to observe the effects of this on the incidence of erythema nodosum.

Two systems of routine oral DDS therapy are in use here, one on a daily, the other on a twice weekly treatment basis. Treatment with " Avlosulfon " Soluble is recommended to be given

on alternate days, but it was felt preferable both on practical grounds and for the purposes of this trial to give the drug twice weekly in a dose of 800 mg. (2 c.c.s), using as a standard of comparison patients receiving oral DDS in the routine but equivalent dose of 400 mg. twice weekly. At this frequency treatment with "Avlosulfon" Soluble would lead to long periods of low blood sulphone concentration punctuated by brief phases of high concentration.

It was not considered necessary to select patients on a basis of long-term observation. Patients with advanced lepromatous leprosy were not chosen, it being considered preferable to choose milder lepromatous and other cases whose normal response to sulphones can be demonstrated unmistakeably within less than a year of starting treatment. There was no difficulty in selecting such patients at random from among those being admitted, leaving others of the same types to take routine oral DDS treatment.

Those selected were classified as follows:—

Lepromatous, moderately advanced ...	4
Lepromatous, early	9
Tuberculoid	8
Indeterminate	1
Borderline	2

Where necessary, the classification was confirmed by biopsy.

All these patients commenced treatment with a dose of 0.5 c.c. "Avlosulfon" Soluble twice weekly, the dose being increased gradually up to a maintenance dose of 2 c.c.s (800 mg.) twice weekly. After nine months the position of these patients was as follows:—

MODERATELY ADVANCED LEPROMATOUS CASES

All four patients showed steady clinical improvement. In two of them clinical improvement was pronounced, and accompanied by a decrease in the numbers of acid fast bacilli in routine smears. From the seventh month, in smears from all four patients, significant numbers of bacilli had degenerated to granular forms.

EARLY LEPROMATOUS CASES

All nine patients showed marked clinical improvement within nine months. In two of them smears had become negative for

acid fast bacilli. In all the remainder there was a definite reduction in the number of bacilli in routine smears, and signifi- numbers had degenerated to granular forms.

TUBERCULOID CASES

In six of the eight tuberculoid cases, macules had become flat and inactive by the sixth month. In the other two progress was good, but had not reached this stage in nine months.

In the indeterminate case, erythema had disappeared and macules appeared residual by the fifth month. In one of the two borderline cases there was rapid and dramatic resolution, and smears were negative within six months. The other showed improvement.

These results may be considered very good. Judged by experience five years ago they might even be regarded as outstanding, but in assessing them it is necessary to bear in mind that patients now seek treatment at earlier stages of their infection than formerly, and in consequence the results of treatment with DDS itself are very good, and becoming better. Nevertheless, the progress exhibited by patients receiving "Avlosulfon" Soluble was quite as good as that displayed by corresponding patients receiving oral DDS. This is evident from the records of 33 patients of similar types admitted during the same period and treated with a standard dose of 400 mg. DDS twice weekly. The progress of these was as follows:—

MODERATELY ADVANCED LEPROMATOUS CASES

Of five cases, all showed definite clinical improvement in nine months, accompanied in all cases with a recognisable decline in the number of bacilli in routine smears.

EARLY LEPROMATOUS CASES

Eleven cases all showed clinical improvement, within nine months, very marked in five cases. All showed a definite reduction in numbers of bacilli in routine smears, and three had become bacteriologically negative.

TUBERCULOID CASES

Out of 17 cases, seven have become inactive in six months, and four more became inactive within nine months. The remaining seven showed marked improvement but were not entirely residual after nine months.

One indeterminate case became residual within eight months. One borderline case showed great improvement and smears became negative within nine months.

There was thus little to choose between the two groups of patients.

Of the 14 lepromatous cases receiving "Avlosulfon" Soluble, only one suffered from typical erythema nodosum, and that not severely. Two early cases, however, displayed an interesting phenomenon, whereby after showing a rapid decline in bacilli in routine smears they suddenly evolved into the borderline type of the disease, with the eruption of numerous macules of typical succulent appearance, the nature of which was confirmed by biopsy. In one instance this change occurred in the third month, in the other in the fifth month. In both cases resolution thereafter proceeded rapidly. In another similar way one borderline case produced a fresh eruption of macules of a definitely tuberculoid nature in the fifth month, with a change in lepromin reaction from negative to positive. There were no other complications whatever among these patients.

ERYTHEMA NODOSUM

With the exception of the four moderately advanced lepromatous cases these patients were not of a type liable to suffer from erythema nodosum. The activity of "Avlosulfon" Soluble in precipitating erythema nodosum was examined in four other patients carefully chosen for this purpose. These were all fairly advanced leproma in type, who after much treatment were all in a phase of marked intolerance to oral DDS, any increase above a low critical dose, individual for each patient, precipitating an attack of erythema nodosum. These four patients were transferred to twice weekly treatment with "Avlosulfon" Soluble, commencing with a dose of 0.25 c.c. (equivalent to 50 mg. DDS) and slowly increasing over a period of weeks. In all four cases it was found that whereas for a short time they tolerated a dose of "Avlosulfon" Soluble corresponding to as much as, or a little more than, the critical dose of DDS to which they were accustomed, sooner or later, and in each case within three months, intolerance appeared and the dose had to be reduced, until in three cases even 0.25 c.c.s precipitated erythema nodosum, and the drug was withdrawn.

The subsequent history of these patients is of interest. One of them continued to suffer from repeated and severe attacks of

erythema nodosum even in the absence of chemotherapy, but after ACTH and a period of rest resumed treatment on oral DDS. The others all took DDS in low doses without difficulty. In all cases, however, marked improvement followed during succeeding months.

DISCUSSION

Although not the least of the many virtues of oral DDS is its simplicity of administration, the giving of sulphone by injection has been advocated by several workers as the method of choice in special circumstances. Such circumstances are of two types. There is first the situation where for one reason or another frequent treatment is impracticable and it becomes desirable to inject sulphone in the endeavour to provide a depot of the drug in the tissues. In such circumstances administrative expediency may justifiably dictate the method of administration used. It does not imply any special therapeutic virtue in injection treatment. It has, however, been claimed by some workers that when administered by injection sulphones have less tendency to evoke undesirable reactions than when given orally. With preparations which release only small quantities of DDS this is readily explained. The patient simply does not receive sufficient DDS to evoke such reactions. With a preparation such as "Avlosulfon" Soluble this cannot be the case. Nevertheless one of the advantages of "Avlosulfon" Soluble is said to be a tendency for patients receiving it to develop less lepra reaction than when receiving oral treatment. If the term lepra reaction is used in its strict sense, none of our patients exhibited it and no comment can be offered. If it includes erythema nodosum of all degrees, it may be stated that among our patients the tendency for erythema nodosum to appear under "Avlosulfon" Soluble therapy was not less than with oral DDS and in some patients was greater. This is what one would expect from the wide range of blood sulphone concentrations with "Avlosulfon" Soluble therapy. It was of importance only in patients whose tendency to erythema nodosum had already made their treatment a difficult problem.

The high therapeutic activity of "Avlosulfon" Soluble when administered twice weekly is of considerable interest, and various explanations may be offered for it. Bearing in mind that for the greater part of each week the level of total sulphone in the blood was below 0.3 mg.% and that of extractable DDS less than 0.2 mg.%, it may perhaps be suggested in the first place that the

sulphone level in the blood which suffices for therapeutic activity is in fact lower than is often believed. Lowe suggested some years ago that a blood concentration of free DDS as low as 0.2 mg.% may be therapeutically active, and that the critical level may indeed be lower. (Lowe, 1952.) There often is virtue, as Muir has pointed out, in doses of DDS considerably lower than those usually employed. Nevertheless, Lowe did notice some slowing down of therapeutic response at a blood level of 0.1 mg.% and it is a matter of clinical experience that in some patients an increase of dose is associated with accelerated resolution of lesions. If an effective low concentration in the blood is the only factor responsible, the rapid response of our patients to "Avlosulfon" treatment is surprising. It is probable that some other factor is involved.

In the second place it may be suggested that virtue exists in the periodic "hammer like" effect of the brief phases of high blood sulphone concentration following each injection of "Avlosulfon" Soluble, which while too brief to lead to toxic signs yet may be sufficient to exert a good chemotherapeutic action. This idea, familiar in some forms of antibiotic and sulphonamide therapy is attractive, but is untenable if it is believed that the active agent is free DDS itself. It was shown earlier in this paper that during the phase of high blood concentration following each dose of "Avlosulfon" Soluble, the concentration of extractable DDS in the blood exceeds that obtained following the corresponding oral dose of DDS only during the first hour, and only by a small amount. The high blood level is due not to free DDS but to soluble derivatives.

This leads to a third possibility. It has yet to be demonstrated how far the chemotherapeutic action of DDS is due to unchanged DDS in the blood and tissues, and how far any water soluble metabolites which may be produced from it in significant amount in the body are implicated. If one of these was active in low concentration, and was also readily synthesised from "Avolsulfon" Soluble, a ready explanation would be forthcoming for the activity of "Avlosulfon" Soluble when administered twice weekly.

Considerable evidence is now accumulating that these products of sulphone metabolism do include active substances. Recently Bushby and Woiwod have obtained evidence that in rabbits DDS is metabolised in part to a monosubstituted compound with

glycuronic acid. (Bushby and Woiwod, 1955.) Similar work on " Avlosulfon " Soluble has yielded evidence of two closely related soluble monosubstituted DDS compounds. (Thorp, 1955.) The antibacterial activity of monosubstituted sulphones is well known, and has indeed been stated to be greater than that of DDS itself. (Smith, M. I., 1949.) If the metabolism of sulphones in the human body proceeds along similar lines to that in the rabbit, the synthesis of active monosubstituted sulphone compounds is likely.

In this connection it is of interest to note the similarity of chemical structure between " Avlosulfon " Soluble and sulphetrone (Solapsone), and also the similarity in the relation of blood levels to therapeutic activity between the two compounds. Sulphetrone has been studied extensively. Dharmendra and his co-workers (Dharmendra, 1950a) found that when given by injection, an aqueous solution of sulphetrone in a dosage of 2.0 gms. twice weekly led to a therapeutic effect comparable with that expected from oral sulphetrone in its standard much higher dosage. Blood concentration of total sulphone followed a pattern similar to that we have found with " Avlosulfon " Soluble. (Dharmendra, 1950b.) Lowe showed that on a injected dose of 3 gms. sulphetrone twice weekly, only a very small proportion appeared in the blood in the form of DDS, yielding a maximal free DDS concentration of 0.12 mg.%. It is thus most unlikely that the very good results reported by Dharmendra on a twice weekly dose of 2 gms. could be accounted for in terms of DDS alone, and Lowe suggested that some other factor, possibly a monosubstituted sulphone may be involved. The work of Bushby and Woiwod gives very strong support to this.

The parallel with " Avlosulfon " Soluble is striking. It lends support to the hypothesis that both these compounds owe part of their activity to water soluble metabolites produced in the body, and which are either themselves monosubstituted sulphone compounds or are a further stage in the metabolism of such compounds. It may very well be asked how far the activity of DDS is due to the production of such soluble products of metabolism, a question of importance in any study of the baffling problem of how sulphones interfere in the physiology of *Myco. leprae* in the human body.

SUMMARY AND CONCLUSIONS

1. " Avlosulfon " Soluble, a preparation introduced for the treatment of leprosy by injection, is a 40% W/W sterile aqueous

solution of a simple disubstituted DDS compound, diethyl diaminodiphenyl-sulphone disulphonate. On injection this is said to break down in the body to release half its weight of DDS.

2. Comparison between the levels of sulphone blood and urine attained after the injection of this substance with those attained after the ingestion of DDS in corresponding dosage shows that "Avlosulfon" Soluble is absorbed into the blood more quickly, but is also excreted much more quickly. A short-lived high sulphone concentration in the blood is thus produced, which falls after a few hours to a low level.

3. If "Avlosulfon" Soluble is dissociated in the body to free DDS, this is only one phase in the chemical actions involved. The parent substance itself appears to undergo complex chemical actions in the body so that at any time not more than 50% of the sulphone in the blood of our patients was in the form of free DDS capable of being extracted by benzene. "Avlosulfon" Soluble behaved similarly, indeed with a dose of 800 mg. the proportion of extractable sulphone during the first few hours was even less. As free "Avlosulfon" Soluble if present would almost certainly undergo hydrolysis during the estimation of sulphone by the Bratton and Marshall method and give a colour reaction, it is not possible to eliminate it as a factor responsible for the large amount of non-extractable sulphone present, nevertheless it is certainly not the only factor.

4. Although the makers recommend that "Avlosulfon" Soluble be injected at 48 hourly intervals, a clinical trial in which it was used on a twice weekly basis yielded very satisfactory results, the progress of patients receiving it during the first nine months of treatment being as good as that of a control group receiving oral DDS in corresponding dosage. Complications during treatment were insignificant, but in a small test group it was not found that "Avlosulfon" Soluble had less tendency to evoke erythema nodosum than the parent compound. "Avlosulfon" Soluble thus appears to have no advantages over the parent compound, but where treatment by injection is desired it is a convenient and satisfactory preparation.

5. The high therapeutic activity of "Avlosulfon" Soluble on twice weekly treatment is interesting in view of the blood sulphone levels with which it is associated. For the greater part of the time the level of extractable DDS in the blood of our patients was less than 0.2 mg.%. While a DDS level as low as

this may very well have virtue, it appears likely that some other chemotherapeutic agent is also operating. The brief phases of high blood sulphone concentration which follow each injection of " Avlosulfon " Soluble are produced mainly not by extractable DDS but by derivatives which are more freely soluble. In view of its being a disubstituted compound, it is not likely that " Avlosulfon " Soluble is chemotherapeutically active, but soluble monosubstituted compounds could be produced during its hydrolysis, and evidence exists not only that such compounds are produced, but that they are therapeutically active. A parallel appears to exist between " Avlosulfon " Soluble and Sulphetrone in this respect, and it appears at least possible that the activity of DDS itself may be due in part to the synthesis of such substances from it in the body.

ACKNOWLEDGEMENTS

My grateful thanks are due to Miss F. McNulty, Mr. G. Okezie, and especially to Mr. S. E. Drewett, for the numerous laboratory estimations entailed by this work, and to patients and members of staff of the Uzuakoli Settlement for their co-operation; also to Imperial Chemical (Pharmaceuticals) Ltd. for generous supplies of " Avlosulfon " Soluble and much co-operation; and also to the Director of Medical Services, Eastern Region, Nigeria, for permission to publish.

REFERENCES

(1) BUSHBY, S. R. M., & WOIWOD, A. J. (1955) Am. Rev. Tub., **72**, 123.
(2) DHARMENDRA (1950a). Lep. in India, **22**, 46.
(3) DHARMENDRA (1950b). Lep. in India, **22**, 178.
(4) DHARMENDRA, DEY, N. C., BOSE, R., and KAPUR, P. L. (1950). Int. J. Lep., **18**, 309.
(5) THORP, DR. J. M., of Imperial Chemical (Pharmaceuticals) Ltd. Personal communication.
(6) LOWE, J. (1952). Lep. Rev. **23**, 16.
(7) MUIR, E. (1952). Trans. Roy. Soc. Trop. Med. & Hyg., **46**, 113.
(8) SMITH, M. I., *et al.* (1949). Ann. New York Acad. Sc., **52**, 704.
(9) TOUZIN, R., and MARLAND, R. (1953). Med. Trop., **13**, 1002.

LEPROSY IN KOREA
PART II

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The Evolution of the Disease

I have already referred to the necessity of studying what I have termed the pattern of the epidemic of leprosy in Korea if we are to approach the control of this disease from a practical point of view. A knowledge of the evolution of leprosy is also of great importance, if we are to devise the most economical means for its control, which, under any circumstances, will be a difficult and complex task. By the term "evolution of the disease' I mean its general development or progression in the individual case and the likelihood of a person who shows early signs of leprosy entering the infective stage or passing on to deformity and mutilation. While it is understandable from the point of view of a communicable disease that stress is placed on infectivity, yet the chances of a person being deformed is a more immediately serious consideration than the mere presence of bacilli, in so far as that person is looked upon as an economic unit. In our study of child leprosy in India we found that 7% of childhood leprosy (and we learned to recognise these lesions very early clinically) did not go on to the more serious forms but became spontaneously arrested. In Africa I have learned that while certain clinical lesions—mostly of the indeterminate macular group—may not always be seriously infective, yet the chances of ultimate deformity are very high unless adequate care is given in the form of physiotherapy and, where necessary, orthopaedic surgery. As a result of the introduction of sulphone therapy there is some danger of complacency, of assuming all is well because sulphones are being administered. In the active lepromatous case blindness may be hastened unless the eyes are carefully watched, and steps taken in time to prevent damage to the finer structures of the eye as a result of reactions. If adequate steps are not taken a person may gradually become terribly multilated, since those in charge of the case are under a false sense of security because the patient is having sulphone therapy. I suspect two things concerning leprosy in the Mongolian race: firstly, the period between the appearance of the

first lesion and progress toward becoming an open case is relatively short; and, secondly, the proportion of true tuberculoid to other types is very low as compared with the African and Indian races. This means that of the total number of cases which progress, the majority become either lepromatous or mutilated or both of these. In order to assess the importance of leprosy and its tendency to self-healing or progression, the natural evolution of the disease in Korea should be studied.

Leprosy Institutions

It is not my intention to describe in detail my visits to colonies and leprosaria in the Southern Provinces, but to discuss in general terms the situation in respect of these as I saw them on my visits to the various institutions, and to draw attention to certain ones which I consider are of greater importance because they may have a significant role to play in the gradual development of a leprosy control system.

Taken as a whole the leprosy institutions are colonies or settlements rather than leprosaria. In my thinking a leprosarium is an institution analagous to a tuberculosis sanatorium, where the disease is treated from every aspect, including the surgical, and there is an adequate full-time medical and nursing staff. It should have a reasonably equipped laboratory for routine and special investigations and be able, if need arises, to undertake at least a limited research programme. I fear there is no such institution in Korea at present. Instead, there is the old mediaeval concept that anyone who has leprosy must be removed as far from human habitation as possible, fed, clothed, housed, treated, but with little hope of return to the community. This has resulted in banishing a a large number of patients, but the main source of infection—the early case in the house—has remained untouched. Further, as a result of this policy, the direction and organisation of leprosy institutions has fallen into the hands of the patients themselves, creating "a world within a world," peopled by persons with leprosy, who have a powerful organisation which is in a position to dictate terms to government. Patients should be enlisted in the campaign against leprosy, for their understanding co-operation is vital to its success. But when the institution is virtually in the hands of the patients, and the doctor and administrative staff act merely as intermediaries between the patients and the outside world, it is detrimental to the building up of a preventive system and harmful to the physical, mental and moral welfare of the

patients. Sorokto Island, an extreme example of this, is a heritage from the Japanese regime. The chief medical work is done by " leprosy doctors " who, from lack of adequate qualified staff, have had only two years' theoretical training. In this connection I must pay tribute to these leprosy doctors, for they apply energy and sympathy to their task, and are learning in the hard school of experience how to cope with situations, both surgical and medical, as they find them.

Specific Treatment

I fear that as a result of sulphone treatment applied by untrained, or partially trained personnel, there is a danger of increased blindness and deformity, as reactions occur for which treatment is not supplied. In other words, sulphone therapy can aggravate eye lesions and increase blindness and hasten the development of deformity if administered without specialist knowledge. Government through KCAC (Korean Civil Assistance Command) sources supplies all special drugs, and special relief funds continue to be expended both for drugs and food. In fact I am told that 90 to 100 per cent of all the special orphanages get food, and KCAC supplies, and in some instances 60 per cent of this is also supplied to institutions. But as outside supplies are unlikely to be continued indefinitely, every effort should be made to make institutions self-supporting as far as food is concerned.

Where the Patients Live

It is not possible to describe all the leprosy institutions in Korea, and therefore I shall select three which illustrate important points.

Ae Yang Wong, the colony on the Soonchun peninsula, was begun by Dr. Wilson many years ago. It is in a beautiful part of the country and is excellently administered. With its medical work reorganised it could develop into a first-class leprosy sanatorium linked to a comprehensive, but limited, pilot leprosy scheme under the over-all direction of the superintendent of the Chonju hospital of the American Presbyterian Mission.

Taegu, also a mission colony, was founded by Dr. A. O. Fletcher in 1919, and is superintended from the Presbyterian Hospital. As an institution it has outgrown its available space, as the town has encroached up to the gates of the hospital. It might be developed but could profitably be reduced in size.

The *National Institution* near Taegu (Ai Song Won) is one of the best institutions I saw. I found a spirit of independence and

initiative which if encouraged could lead to the development in due course of a modern leprosarium. The usual weaknesses were present: lack of adequate medical supervision, irregular and uncritical supply of drugs, but the spirit of the place augurs well for the future.

In addition to the colonies and settlements there are numerous leprosy villages where patients have gathered and formed a community life of their own. There has been general support of these villages, for through them patients are receiving sulphone therapy. Unfortunately, the majority of these villages are no more than hovels on the outskirts of towns in which patients gather together and organise themselves into some kind of society for protection and companionship. More than fifty years ago Dr. Noble Mackenzie, and later Dr. Wilson, seeing the miserable plight of these people, started leprosy colonies to rescue them from living a life of mendicancy and dwelling among the graves, a people of the living dead. But the dramatic results of sulphone therapy, combined with war-time difficulties, and the migration of large populations, led leprosy patients once again to gather together and put up a few shacks, or live under bridges and make their living by begging. Seeing their sorry plight, government, with the aid of voluntary organisations, helped them to resettle in areas which, generally speaking, were poor, and supplied them with food and drugs in the hope that they would in due course recover through sulphone therapy. The reasoning seemed sound, but I fear that owing to the advancement of their disease, the irregular and intermittent supply of sulphone drugs, and the psychology of the patients, the experiment cannot be described as an unqualified success. This does not mean that all leprosy villages need to be condemned, or that there is not a place for such a scheme in the over-all plan of control.

In order that a general picture of these villages may be given I will describe from my notes two villages, one a well-run colony and the other a tragic group of pathetic people. The first village I should like to describe is that of *Yong Yin* (near Seoul). In 1952 a group of approximately 18 patients established themselves under a bridge, and afterwards secured some land and developed under their own initiative, with the help of the KCAC team, a model village. The village, or rather colony, is on an excellent site, the houses well built, and the patients industrious; in addition to agriculture they are going in for poultry in a big way. The leader of the colony, an educated man, with a strong

personality, works with a committee who choose the cases for admission, and as a result there are remarkably few really advanced or crippled cases. The patients themselves seem prosperous enough to buy their own supplies of sulphones, but government is supplying drugs, though intermittently. The colony itself is almost self-supporting and has a population of 150 persons. The intention is to keep the numbers within manageable proportions, and there would have to be strict selection so that the community, owing to the admission of advanced cases, does not become pauperised because there are not sufficient able-bodied persons to maintain the economy of the village.

In contrast with this is the village of *Sang Nak Won*, on the outskirts of Mason, a collection of hovels on the hillside among the graves. Sulphones are being supplied irregularly and intermittently, but the pathetic reliance on sulphones is tragic and disturbing to witness. The patients eke out their miserable existence by begging, and who can blame them? Thus they add fuel to the fire of hate engendered in the well villagers' hearts for these people.

Work among Children

In every report I have read with reference to leprosy in Korea the attention of the authorities has been drawn to the large number of apparently healthy children living with infectious parents. The situation has arisen as a result of permitting marriage in leprosaria. It is unfortunate and exceedingly detrimental to the development of a sound anti-leprosy scheme to permit large numbers of apparently healthy children to live with infectious parents. The place for these children is in special observation homes not too far away from the institution, from which, after an adequate period of observation and treatment, they can be returned to relatives in their village, discharged with their parents if they are healed, or sent to one of the many homes for destitute and unwanted children which are such a tragic feature of Korea since the war.

It must be said that while there are many apparently healthy children in the leprosaria, there is some attempt to send them to preventoria. The right course is to take young children from their leprosy environment and bring them up as normal children. Unfortunately the children are separated too late, at 3 to 5 years of age, after infection has already occurred.

Preventoria

I will not describe orphanages individually. They are somewhat like leprosy villages, some well run, some poor, and many

rather shabby and miserable. KCAC supports the orphanages entirely and there is a generous supply of food, and in many cases CARE packages. In some orphanages the children go to the ordinary school, while in others there is no such provision. In all there is a vagueness about plans for the future of the children which, to say the least, is disturbing.

Dr. Crane, of Chonju, has shown the way to deal with such a situation. He takes the babies from the Dr. Wilson Colony at birth and places them, not in a healthy children's home or preventorium, but in an " unwanted babies " ward where destitute and abandoned babies are cared for. He tells me there is no difficulty in getting these babies adopted.

The preventoria are not really preventoria in any real sense. They are what we called in India observation homes. The children have all been so grossly exposed to infection that the number of children showing signs of early leprosy is probably between 5 per cent and 30 per cent. I was rather surprised in one or two institutions to discover on superficial examination a significant number of children with very early signs of infection. Here is a rich field for research in early lesions of leprosy, and for confirming the Bombay work on contacts of open cases. Every child that is proved healthy should be brought up in an environment free from all suggestion of leprosy, and the place for such a child is in one of the numerous ordinary orphanages, not in a special one for children of leprosy patients, for by building special orphanages we just encourage the development of this " world within a world " which is so tragic. Let us not make the unwanted child's life still more tragic by perpetuating a leprosy tradition, and so guaranteeing that he will never be absorbed into society, but must for ever bear the name of " leper."

Principles of Control

I have tried to outline the present position with regard to leprosy in Korea and this, naturally, leads up to the question, " Is it possible to control the disease within a measurable time? " If we are to succeed in our ultimate objective, the control and elimination of leprosy, I see no other approach except that of Public Health. I have, therefore, recommended that the first step in organising an anti-leprosy campaign throughout the land is to appoint a Public Health Officer, whose specific duty is to investigate the epidemiology of leprosy as seen in Korea, and determine what is the best method of control. This officer need not

be a leprologist, but he should receive a preliminary briefing in leprosy to enable him to understand his task. Having selected the Public Health Officer his specific task would be to study leprosy in relation to the general principles of control in chronic infectious conditions. He would study the nature of leprosy in South Korea, and particularly investigate the contention that if the disease is controlled in the house it will be generally controlled in the country. Another task would be to ascertain the true infection rate in sanatoria, colonies and preventoria, particularly the open case rate.

While systematically visiting the field, particularly in the Provinces of Kyongsang Namdo, Kyongsang Pukto, Cholla Namdo and Cholla Pukto, he would through contacts with local authorities, missionary workers, etc., get opportunities to examine groups of people, particularly school children, and in the course of time would be able to complete the examination of a fair sample of the population, and therefore the opportunity would arise to confirm or deny the estimate that the incidence of leprosy, particularly among school children, is around 10-12 per thousand of the population.

Voluntary Organisations

A further step in the building up of an efficient anti-leprosy system is to use voluntary organisations to prepare the way for Government to take and run the leprosy work on a country-wide basis, the control of leprosy being the inescapable duty of the National Government. In all this work there must of necessity be a close liaison with the Ministry of Health and Social Affairs and, therefore, it would be advisable to select early a national doctor, who is familiar with the English language and deeply interested in Public Health, to be a colleague of the Public Health worker appointed to study leprosy.

One of the main tasks of voluntary organisations such as the American Leprosy Missions, the Mission to Lepers, London, and the American-Korean Foundation, is to investigate, with the co-operation of KCAC, and the active approval and support of government, the possibility of setting up a pilot scheme with a view to assisting the government in formulating a comprehensive programme of leprosy control. This pilot scheme would be a demonstration to the government in one area of the principles of leprosy control, and indicate how leprosy can be integrated with the general medical programme of the country. These principles could then

be extended gradually throughout the country and it might be possible to control leprosy within the foreseeable future.

As far as I can see there are two fields in which demonstration of the correct methods of approach can be set up. These are (1) a small but comprehensive scheme illustrating the over-all approach to the leprosy problem; (2) a demonstration of the part a general hospital can take in dealing with this problem.

Pilot Project Illustrating Modern Approach to Leprosy Control

In choosing an area for such a demonstration and ultimately a training centre, there are certain prerequisites: (a) a relatively highly endemic area; (b) the possibility of continuity over a period of years; (c) an institution which could be developed into a modern leprosy sanatorium demonstrating every aspect of relief; (d) a general hospital in the vicinity so that the leprosy work can be included in the over-all medical programme. The personnel of this institution, and especially the senior medical staff, would be willing to undertake leprosy work and co-operate in the project.

It will be well understood that under the present circumstances the group that can fulfil most nearly the above prerequisites is a group in the missionary community. There are two areas, both in provinces of relatively high endemicity, where most of these conditions can be fulfilled. One is at Soonchun with the nearby Wilson Leprosy Colony and, serving this same field, an excellent hospital under Dr. Paul Crane at Chonju. Both these institutions belong to the Presbyterian Church, and the missionaries are members of the so-called " Southern " Presbyterian Mission of America. Another institution which fulfills many of these conditions is the American Presbyterian Mission (North America), and the centre of this mission's medical activity is at Taegu. It therefore seems to me possible to visualise the leprosarium at Soonchun developing into a teaching and training centre, and the institution at Taegu being tied more closely to the hospital.

Soonchun. In order that this unit may develop adequately it would be necessary to place a doctor in charge of the leprosy colony and build a house on the outskirts of the colony in which he could settle with his family. I would not propose that a new missionary, when he is recruited, be placed in charge of the Soonchun Leprosarium at once. I have therefore suggested that if, as I believe probable, another missionary doctor is recruited for the Presbyterian Mission in this area particularly to develop

leprosy work, he be given a briefing along similar lines to that which will be suggested for the Public Health Officer, but somewhat more inclusive and more detailed. He should be first stationed at the hospital at Chonju and share the supervision of Soonchun with the medical superintendent for six months to two years, the time depending on his aptitude for the language and his previous general medical experience. Whatever the period, he would first learn to relate leprosy to the general disease problems of the country and then be stationed as medical superintendent at a leprosarium. This step is absolutely essential if, as it should be, the determined policy is to train national doctors to undertake leprosy work.

Chongju. The advantage of selecting Soonchun for this purpose is that at Chongju in addition to advanced surgery being undertaken there is a unit for rehabilitation of physically handicapped persons, and there is a plan for adding a physiotherapist to the staff of the hospital, who could direct this side of the work at Soonchun, teach a patient or patients to supervise the exercises necessary to prevent or relieve deformity, and teach those patients who have severe nerve dysfunction how to care for their hands and feet and how to prevent injuries and unnecessary trauma.

Demonstration of the part a General Hospital can take

A general hospital is prepared to accept for admission tuberculosis cases if temporary, emergency treatment, medical or surgical, is needed. It is also prepared to treat certain severe acute infective conditions such as typhoid, dysentery and the more chronic infective condition, syphilis; and yet, if a case of leprosy seeks temporary admission for some condition needing immediate medical or surgical care, the doctors hesitate very greatly before admitting such a case. Yet there is far less risk or danger to the other patients in the case of leprosy than of these other diseases.

Taegu. Taegu Hospital has the opportunity of setting the example in this respect and of integrating leprosy into the ordinary hospital programme. Leprosy is as much the responsibility of the department of internal medicine as tuberculosis, and the tuberculosis department might co-operate in investigating the question of leprosy in the follow-up and search for cases of tuberculosis. The opportunities in this hospital to set an example in the discovery of cases of leprosy are very great. There is also a well-trained technician in charge of the laboratory and he could develop the laboratory side of this work and train a leprosy technician to do

the routine laboratory work and he himself develop specialist laboratory techniques—skin tissue sections, Mantoux and lepromin tests, and B.C.G. vaccination if indicated.

In addition to this short-term plan, briefly outlined, there was presented to Government a long-term plan, and the hope was expressed that such a plan would become truly indigenous—rooted in the soil—for foreign aid should only be given in order to help set up a thorough, scientific, and national Specialist Leprosy Service, covering every aspect of leprosy—prevention, treatment, education, social welfare, child care, vocational training and rehabilitation. Once this Service is established there will be great hopes that leprosy as a serious endemic disease will be brought under control.

I came away from Korea convinced of the sincerity of all voluntary organisations, and of Government, in their efforts to combat leprosy.

CORRESPONDENCE

The Editor of Leprosy Review.

London.

Dear Sir,

Some time ago I read an article in the Leprosy Review telling of a seven months' old baby having contracted leprosy.

During this year at the Leper Colony Luampa, Mankoya, we have been treating a baby of four months. The child was born last December and the mother brought him to the clinic in March. There were several macules on the left buttock and leg. Several smears were taken and they were all positive.

I wrote to Dr. Garrod, N. Rhodesia, and he advised me to write to you. The father of the baby is in Geomiston and hasn't seen the child. His mother had leprosy but died some years ago; his aunt is a leper and lives in the village near the baby. The grandmother of the wife is a leper but does not live near the baby. The baby is a bonnie child and seems most healthy apart from the macules.

I'm sorry for the delay in writing but I have come over to England for a few months' holiday.

Yours faithfully,

F. WATSON (Miss),

Sister-in-charge.

Leper Colony,
Luampa.

REVIEWS

Experimental Tuberculosis and Leprosy*

In October 1954 an international group of chemists, pharmacologists, pathologists, bacteriologists, immunologists and tissue-culture experts engaged in tuberculosis research met in conference in London. They were the guests of the Ciba Foundation, who had organised a symposium on experimental tuberculosis and leprosy.

The meetings lasted two and a half days, two days being devoted to tuberculosis and the last half day to papers on leprosy. Twenty-two papers were read on the former disease and four on the latter, each paper being followed by discussion. These papers and discussions have now been published in a volume of about 400 pages, and should be of immense value to all experimental workers in both diseases.

(1) Of the four papers on leprosy the first is by M. B. Lurie on the *Pathogenic Relationship between Tuberculosis and Leprosy.*

Tuberculosis has a " symbiotic phase " when there is an early diffuse accumulation of monocytes with coarsely vacuolated cytoplasm harbouring many bacilli in symbiosis with uninjured host cells. This is followed by a " nodular phase " in which mature epitheloid cells with very finely vacuolated cytoplasm are collected in tubercles and at the same time there is destruction of many intracellular mycobacteria. This latter phase is characterised by cell death and caseation and tuberculosis sensitivity. Lepromatous leprosy corresponds to the former of these phases and tuberculoid leprosy to the latter. Thus the pattern of tissue response to different mycobacteria in different species, including those of human leprosy, appears as variants of a common theme. This theme varies with the predominating growth or destruction of the bacteria and the meagre or marked development of allergic sensitivity.

(2) J. Lowe in his paper on *The Leprosy Bacillus and the Host Reaction to it,* mentions a " curious dichotomy in the manifestations of leprosy infection." In the two main types there is sensitization and immunity on the one hand and complete lack of these on the other; while in tuberculosis there is an " interplay

* Experimental Tuberculosis, Bacillus and Host, with an Addendum on Leprosy. Edited for the Ciba Foundation by G. E. W. Wolstenholm and M. P. Cameron. J. & A. Churchill Ltd., 42s. shillings net.

of findings, some indicating the invasive powers of the infection and some indicating sensitization and resistance of the host tissues." In the lepromatous case with abundant bacilli but no cellular reaction to them, circulating antibodies are easily demonstrated, but no sensitization, no cellular antibodies revealed by the lepromin test, and no resistance to infection. While in the tuberculoid case, with limited lesions and very few bacilli, but intense cellular reaction to these few bacilli, circulating antibodies are difficult to demonstrate, and there is apparently a high degree of sensitization and immunity to the infection.

Protein desensitization may be effected without impairing cellular response to the whole bacillus, as shown by the delayed Mitsuda reaction, so that the response to the whole bacillus and not to any fraction appears to be the main factor in immunity.

(3) The paper by R. G. Cochrane is a short review of the *Reaction of the Host Tissue to Myco. leprae.* He describes the tissue reaction in the various types of leprosy, discussing particularly two views regarding the nature of the lepromin reaction: (a) that the allergic response determines the type of leprosy, (b) that the type of leprosy determines the allergic response. A permanent cure depends on the ability of macrophage cells to develop an environment which prevents re-multiplication after the number of bacilli has been sufficiently reduced by sulphone therapy.

(4) J. H. Hanks writes on *Immunological and Physiological Basis of Immunization in Tuberculosis and Leprosy.* Diseases like tuberculosis and leprosy are chiefly confined to those in whom immunological response is slow or poor. Therefore attempts at immunization should be confined to identifying and immunizing the poor responders. The difficulty of the tuberculoid patient is not that he cannot make an immune response, but that he achieves this response rather slowly. Had he been previously immunized he might not have had leprosy at all. The question of a mixed vaccine of B.C.G. and dead *Myco. leprae* is mentioned. It is suggested hypothetically that when B.C.G. is injected in a more resistant patient the bacilli may be more promptly destroyed; while in the more suspectible persons (requiring more antigen) the bacilli may not be destroyed so quickly and may thus produce more antigen.

Among the papers and discussions on tuberculosis there were many points raised which may suggest lines of investigation in leprosy: some of the more important of these are abstracted below.

(5) M. Stacey, writing from the chemist's point of view on *The Proteins of the Tubercle Bacillus*, begins with the observation: "The tubercle bacillus is an amazing chemical factory producing in the living cell and in culture fluids a wide variety of chemical substances. Other members of the acid-fast mycobacteria are no less prolific or complex." He then goes on to describe a new method for obtaining a biologically active protein, termed U.C., from live tubercle bacilli by urea extraction in a manner whereby extensive degradation is avoided. He expresses a hope of obtaining even better protein products of great selective diagnostic value.

(6) J. Asselineau and E. Lederer write on *The Structure and Activity of Mycolic Acids.* The number of these varies in different mycobacteria from 2 to 4. They have high molecular weight and contain about 88 carbon atoms. Most of them are lipopolysaccharides (wax D). Fractions of these vary in different strains of mycobacteria. Mycolic acid is the only definitely acid-fast compound isolated from mycobacteria, but this rôle is believed to be an "indirect one, by participating in the formation of an impermiable film round the cell." It is suggested that fuchsin is probably linked as a complex salt to the carbonyl and hydroxyl groups of mycolic acids. Virulent and avirulent strains of tubercle bacilli can be differentiated by shaking up with a buffered solution of neutral red, virulent bacilli acquiring a red colour, and avirulent or saprophytic bacilli only a yellow colour. Injection of mycolic acids has been found to cause persistent necrotic lesions with formation of giant cells.

(7) F. L. Rose and G. A. Snow write on *Mycobactin: a Growth Factor for Acid-fast Bacilli.* This substance is prepared from *Myco. phlei* with the object of providing a growth factor for mycobacteria on the lines of the early work of Twort and Ingram in growing *Myco. johnei.*

(8) M. Stacey in his paper on *Polysaccharide Components of the Tubercle Bacillus* describes two polysaccharides present in most bacteria, the capsular and the somatic. The capsular, which often diffuses into the culture medium, varies chemically and serologically with the type of bacterium, while the somatic is more a common component to all. In *Myco. tuberculosis* the polysaccharide components are unusually complex, eight different structures being known. Three polysaccharides present in the culture filtrate are described. The importance of polysaccharides associated with lipids is being more recognised in regard to eliciting of skin and

cellular reactions and in immunity generally. Attention is drawn to the fact that the " lipid-bound " polysaccharide of mycobacteria bears a superficial resemblance to that of streptomycin, which latter could be imagined as a possible blocking group inhibiting the biosynthesis of certain of the tuberculosis polysaccharides. There are new prospects opened up in attempting to decide how streptomycin inhibits *Myco. tuberculosis* growth, and why resistance can be so easily gained to streptomycin.

(9) A paper by J. Ungar on *Granuloma-producing Properties of Synthetic Fatty Acids* was followed by an interesting discussion on various substances that produce caseation and granuloma, the remarkable fact being that something so small as a single tubercle bacillus can cause a tubercle, whereas comparatively colossal amounts of fatty acids are necessary to produce the same effects.

(10) A. A. Miles writes on the *Early Tissue Reactions to Tubercle Bacilli and their Products.* He shows that tubercle-inoculated animals with very early tissue responses show high survival value in rapidly growing pathogens, such as staphylococci and this is so to a lesser degree in defence against mycobacteria. His method is to follow bacterial inoculation with injection of adrenalin or Liquoid, which have the effect of temporarily inhibiting defence reactions. The sizes of the lesion diameters are then compared with controls without an inhibiting agent. He shows that decisive responses may be established very early before visible histological changes take place.

(11) J. G. Hirsh discusses the *Biochemical Factors which may influence the Fate of Tubercle Bacilli.* Various substances may be contained in certain organs of the body in some animals as compared with others and determine the growth of bacilli in these organs. Retention of carbon-dioxide and accumulation of organic acids may exert an effect on acid-fast bacteria. Spermine and basic peptides are among the substances mentioned as unfavourable to tubercle bacilli.

(12) H. Bloch, in *Bacterial Components concerned in the Early Phase of Infection,* discusses the " cord factor " which is partially responsible for the virulence of tubercle bacilli, and is present in various amounts in the bacilli. The physico-chemical properties are mentioned. Injection of this substance within 72 hours prior to infection turns a mild into a severe form of the disease, and when mice with chronic stationary tuberculosis are injected it makes the infection flare up and become rapidly progressive.

(13) S. V. Boyden and E. Sorkin write on the *Serological Activity of various Fractions of Culture Filtrates of the Tubercle Bacillus.* After chemical fractionation of the filtrates, the method of Middlebrook-Dubos was used for haemagglutination, and tests were made with tanned red cell haemagglutination and haemagglutination by mixtures of antisera and antigen. Precipitation in agar was practiced by Ouchterlony's method. The results obtained stress the great complexity of these culture filtrates, but no attempt has been made to attribute any of the serological activities of the various fractions described to any one single substance, nor is it known whether the serological differences between the various antigenic constituents of culture filtrates are of any special significance in relation to tuberculous disease or type specificity.

(14) C. N. Iland and D. B. Peacock read a paper on the *Serology of Tubercle Polysaccharides.* The results of their own experiments, and those of Dr. Pound, " suggest that the haemagglutination test is either an enhancement of a non-specific reaction or it is a complex phenomenon. In either case it does not provide evidence of the presence of anti-polysaccharide antibody, or of any antibody-antigen reaction until further proof is available."

(15) S. Raffel, J. Asselineau and E. Lederer write on *The Chemical Nature of the Lipoidal Factor of the Tubercle Bacillus responsible for the Induction of Tuberculous Hypersensitivity.* They conclude that it is likely that the peculiar ability of these lipids to take part in the induction of tuberculin sensitivity when injected into guinea pigs along with tuberculoprotein resides in the esterified mycolic acids. Wax D, the most active of the fractions, is a mycolic acid-polysaccharide ester.

(16) A paper by R. L. Mayer on *Tubercle Bacilli as Immunological Adjuvants* leads to the conclusion that various adjuvants, including tubercle bacilli, may *increase* the number and degree of sensitizations of the delayed type, but that they *do not modify* the type of sensitization towards a particular antigen or following a particular mode of sensitizing procedure. An interesting discussion followed this paper on possible reasons for the differences in allergies of the delayed and immediate types.

(17) E. Suter read a paper on the *Relation between Growth Inhibitory Property of Monocytes for Tubercle Bacilli and Hypersensitivity to Tuberculin: An in Vitro Study.* He shows that, although growth inhibition by monocytes and delayed hypersensitivity to tuberculin appear at approximately the same time

after vaccination, the indication is that the growth inhibitory property resulting from vaccination is independent of demonstrable hypersensitivity, and that hypersensitivity can have a depressive effect on growth inhibition by monocytes. In an *in vitro* system there is a delicate balance between phagocytes and tubercle bacilli. Hypersensitivity, as well as large numbers of bacilli within the cells, seems to favour multiplication of tubercle bacilli, whereas small numbers of bacilli and hypersensitivity allows full effect of the inhibitory power of the cells. Unfortunately, there is as yet no way to control consistently all these variables *in vitro*. The tubercle bacillus seems to exert a toxic action only from within the cell and not from without, as cells outside bacilli in infected tissue cultures were not affected.

(18) G. Brownlee and D. G. Madigan write on *Tuberculous Hypersensitivity and Desensitization.* Three groups of subjects were chosen: (a) 4 Mantoux-negative nurses, (b) 4 patients who had been desensitized with graduated daily intramuscular injections of OT and bacillary emulsion, (c) Mantoux positive tuberculous patients. In all these groups 0.1 ml. BCG vaccine was injected and they were challenged with 1 in 10 Old Tuberculin 51 days later. The results are shown in photographs. The BCG nodule was similar and moderate in the first two groups, but there was severe ulceration in the third group. The results are shown clearly in photographs. The authors believe that complete and effective desensitization to skin-challenge has been achieved.

(19) E. M. Brieger's paper on *Tubercle Bacilli in Infective Tissues grown on Tissue Culture* raises the problem of the discrepancy between the small number of bacilli found in early lesions and the extent and severity of the lesions. Why should there be an apparent suppression of growth *in vivo,* while in tissue cultures there is immediate intra-cellular growth? The question is raised whether more bacilli are present in the tissues during the early period after infection than can be shown by ordinary staining methods. Can the bacillus take a form other than an acid-fast rod? Evidence is given of a granular form similar in size to Much's granules, and that non-bacillary structures isolated in the parasitic stage from infected tissues require the living cell for the restitution to the bacillary form.

(20) M. Bloch writes on *The Rôle of Bacterial Multiplication in the Establishment of Immunity to Tuberculosis.* He found that when living preparations of different strengths of BCG were com-

pared, the resulting immunity they produced was proportional to the number of living bacteria contained in the vaccine. The experiments mentioned show that multiplication of the bacilli in the host is not essential for a vaccine to be effective, non-multiplying H37Ra being as effective as multiplying BCG. Immunity in animals was noticeable 3 to 6 days after BCG vaccination, and reached its peak in 3 to 12 weeks, almost completely disappearing 9 months after vaccination.

(21) M. B. Lurie and P. Zapparodi write on *The Mode of Action of Cortisone on the Pathogenesis of Tuberculosis and its Implications for the Nature of Genetic Resistance to the Disease.* When virulent human type bacilli are inhaled by hormone-treated rabbits, three or four times as many primary tubercles are produced as in controls of the same litter without hormone. But the tubercles are smaller and swarm with more bacilli than in the controls. There is excessive accumulation of bacilli within the phagocytes of the treated rabbits, and a corresponding modification of their tissue response. It appears that the digestive capacity of the phagocytes of the treated rabbits is impaired as the maturation of epithelioid cells (a sign of intracellular disintegration of bacilli) is impaired, and there are many bacilli within immature coarsely vacuolated cells. The phagocytic power of the cells is not impaired but their power to limit bacillary multiplication. Whereas in the untreated controls epithelioid cells mature more readily as indicated by the extremely fine cytoplasmic vacuoles, and the persistence of very few bacilli within them. It is concluded that resistant animals are *ab initio* a poorer medium for the growth of bacilli before specific antibody formation is demonstrable; this greater initial inhibitory property of the macrophages of the resistant animal is followed by a more rapid development of acquired specific resistance; acquired resistance is superimposed on and determined by native resistance. Cortisone reduces the fragility of capillaries and protects them against agents which increase the permeability of their walls; the inflammatory response to tuberculin is markedly reduced, and a barrier is interposed between the injured cells and the circulation. Possibly the altered hormone balance, by interfering with the internal metabolism of the macrophages and by reducing antibody formation, affects the site of antigen-antibody interaction, the caseous focus, so that the latter fails to proceed to its completion

(22) *The Mechanism involved in Acquired Immunity to Tuberculosis* by S. Raffel. Evidence of three kinds is brought forward,

all of which have failed to reveal any indication that antibodies or other humeral factors serve as instruments of defence in tuberculosis. All available serological tests have failed to show more activity in sera from immune animals than in sera from animals treated with bacillary components, and which failed to show immunity. Infected animals receiving either immune serum or immune whole blood derived no benefit from these derived substances. A third line of experimentation was to place plastic capsules with a Gradacol membrane at the end, and containing virulent tubercle bacilli, in the peritoneal cavities of normal and immune guinea pigs. There was failure to find any distinction between the multiplication of bacilli in capsules implanted in immune animals and subjected to its humours, and those implanted in normal animals. There was also found to be no distinction under reduced oxygen tension. Thus, although it seems quite probable that immunity to *Myco. tuberculosis* is not dependent upon an antibody-leucocyte relationship, the nature of this mechanism is still unresolved.

(23) *Human Lung Tissue Reactions to the Tubercle bacillus in Relation to Chemotherapy.* In this paper G. Canetti describes histological appearances found in 70 out of 117 cases of pulmonary tuberculosis in lung tissue excised surgically. There was an apparently paradoxical appearance in that in patients who had been treated with chemical agents, particularly isoniazid, there was a temporary increase in the specific cellular metaplasia (epithelioid and giant cell formation). In patients who had not been treated with these chemical agents the lesions were comparatively discrete. In the former there were very few or no bacilli. The explanation given is that the specific cellular metaplasias are due to disintegration of the tubercle bacilli in the centre of the macrophages caused by the bacteriostatic or bactericidal action of the chemical agents.

(24) P. D'Arcy Hart and R. J. W. Rees write on *Influence of Certain Surface-Active Agents on the Host-Parasite Relationship in Experimental Tuberculosis.* Various non-ionic surface-active agents are described, the starting material of which is *p-tert*-octyl phenol. Three of these used were known respectively as D_2—, LOC—, and HOC—. These were found to have an anti-tuberculous effect using members with 10 to 20 ethylene oxide units; but when the ethylene units were increased to 25 to 30 therapeutic activity was abolished; when increased to 45 to 90 there was a protuberculous effect. The hypothesis is that these surface-active agents influence

tuberculous infection by modifying the surface lipids of the tubercle bacillus within the monocytes. Whatever their mechanism, it seems clear that they enter the monocytes and probably provide a means of artificially influencing the operation of the cellular defences in tuberculous infection.

(25) *The Relationship between the Growth Requirements and the Pathogenicity of Isoniazid-resistant Mutants of Tubercle Bacilli: A Study of the Role of Host Physiology in Susceptibility to Infectious Disease,* by G. Middlebrook. It is suggested that INH in adequate dosage achieves " physiological imprisonment " of tubercle bacilli in the tuberculous-allergic animal in a three-fold fashion. It inhibits the multiplication of drug-susceptible organisms and may sterilize them. It loses this direct anti-microbial activity only when the parasite suffers genetic loss of a physiological function which is apparently essential for its full pathogenicity. Its continued administration not only attacks the natively susceptible parasite, which may at any time be given an opportunity to multiply after long periods of metabolic quiescence in necrotic lesions; it also attacks any drug-susceptible reverse mutants which may make their appearance from drug-resistant populations.

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Chaussinand, R. La lèpre. 2nd Edition. 310 pp. 1955.

This new edition of Dr. Chaussinand's well known book on leprosy is enlarged from 212 to 310 pages. It has broader pages, better type and binding, and in place of 75 figures, has now 130, of which 18 are in colour. There are 8 new sections on immunological and serological tests, classification, and epidemiology. The section on treatment is almost entirely rewritten, and chaulmoogra oil, instead of appearing as the principal treatment, is now relegated to the position of an acceessory, useful in producing aesthetic results in some tuberculoid lesions, and in painful neuritic conditions. The treatment of choice is DDS given daily by mouth, the maximum dose being 2 mgm/kg. of body weight. Only if this daily treatment is not possible should weekly or bi-weekly (oral or by injection) treatment be resorted to.

The thiosemicarbazones are mentioned as the second basic form of treatment, to be used only temporarily in those intolerant to DDS.

The clinical section is very clear in its descriptions and illustrations of the various forms of lesions. The " borderline " case, seldom understood, is plainly described, and it is said to yield more readily to treatment than the major tuberculoid.

In the section on prophylaxis the theory of relative crossed protection between tuberculosis is argued clearly and at length. The use of BCG for prophylaxis in leprosy should be studied especially in regions where the endemicity of leprosy is high, or the future extension of tuberculosis is a grave menace.

This book is strongly recommended to all engaged in leprosy work and who are able to read French. The arrangement is convenient, the style clear, and the photographs of cases with the descriptions alongside make it easy to understand the appearances and nature of leprosy lesions. The author has gathered his information and many of his illustrations from those engaged in leprosy research all over the world, and has woven these together with his own wide experience of leprosy in Indochina and in France into a clear picture of the disease in all its aspects.

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Dubois, A. La Lèpre, Diagnostic et Traitement. 72 pp. 15 figs. (1 coloured), 1955. Anvers, Belgium.

The author writes from his long experience of leprosy in the Belgian Congo, where the campaign against leprosy is being pursued with great vigour, and the Government has supplied large quantities of sulphones for treatment and appointed a number of leprologists. The Red Cross and the Father Damien Foundation are also extending their activities and there is thus the need of a book which gives the essentials about diagnosis and treatment simply and clearly. After a few paragraphs on history and geography, etiology is discussed shortly. Under pathology the man-bacillus relationship is treated under 5 classes of subjects: (1) Refractory subjects in whom there is complete escape from the disease, the role of tuberculosis in bringing this about has yet to be established; (2) those in whom the infection is latent; (3) those in whom there are only a few macules of doubtful nature and who are regarded as "suspects"; (4) those with few bacilli and a benign form of the disease, generally classified either as tuberculoid or indeterminate, and of whom consist 80 to 85 per cent of cases in the Belgian Congo; (5) malignant leprosy with many bacilli. The descriptions and illustrations combined make it easy to recognise the different kinds of lesions, and diagnose leprosy from other diseases and classify the different types. Exception is taken to the Madrid Congress classification which includes all non-lepromatous flat lesions as indeterminate; many of these should be designated "simple". An adequate account is given of treatment, DDS being recommended as the drug of choice.

Prophylaxis is dealt with shortly in one page. In the Appendix such subjects as staining, lepromin, leprosy of the eye, estimation of sulphone concentration, treatment with iron preparations, are explained in more detail.

The author makes no claim to have written a textbook, but he has succeeded well in accomplishing his object of supplying clearly and concisely all the information necessary for diagnosing and treating leprosy.

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International Journal of Leprosy, Vol. 23, No. 1, Jan.-Mar., 1955.

S. N. Chatterji writes on *The Mechanism of the Neural Signs and Symptoms of Leprosy.*

He is not satisfied with the usual explanations given of the causes in leprosy of hypopigmentation, anidrosis, keratosis, depilation, loss of sensation, paralysis and trophic ulceration, namely that they are due to degeneration of various types of nerves. He puts forward the hypothesis that most of these are due to diminution of blood supply to the nerves or to the skin and its appendages. As evidence he mentions the improvement of sensation after engorgement of the skin during reaction, or after oil or saline injections, or with passive congestion after tying a binder round the leg or thigh. The temperature of anaesthetic areas was found to be lower than in those with sensation. It is suggested that diminished blood supply to the nerves may be caused by pressure of a thickened nerve sheath on the vasa nervorum, pressure from cellular infiltration between the nerve fibres on the vasa nervorum, or pathological changes in the blood vessels of the nerve.

Thiosemicarbazone as an additive in the Treatment of Leprosy, by A. R. Davison.

The difficulties are described in the trial treatment of 50 patients on thiosemicarbazone (TB-1). Of the 50, there were three deaths from other causes, three absconded, all the thirteen Europeans at their own request had to be transferred to combined treatment including sulphones. The whole project was stopped in April 1954 (after 3½ years' treatment) and would have been stopped sooner had it not been that changes in the morphology of the bacilli encouraged continuing longer. The results in the six tuberculoid cases were fairly satisfactory, as all were discharged in the end, but the results were slower than would have been expected with sulphones. Of the 37 lepromatous cases who continued the treatment, though there was clinical improvement in between three months and a year, and ulceration of the limbs and

larynx healed, only four became negative; but all of these had been taking sulphones, three of them for six years and the other for three years. It is considered that in lepromatous leprosy its action is weak, and in combination with sulphones the two drugs appear to be antagonistic.

M. Blanc and M. Prost write on *Clinical and Therapeutic Study of an Antigen Prepared with Mycobacterium Marianum, Applied to 457 Leprosy Patients.*

The results obtained in producing 73.3 per cent of positive Mitsuda reactions with injections of this antigen in six months to one year, led the authors to apply these injections to all new cases that came under their care. The present report is on 457 patients, 50 per cent of whom were formerly on sulphones combined with the antigen, though later the sulphones were omitted. 0.1 c.c. of the antigen is injected intradermally on the outer side of the left arm once a month for three to six months, followed by two months rest. A local, focal and general reaction results with fever, headache for two or three days, and with burning at the site of injection and a papule which increases up to the 28th day, forming a nodule which may become 2 to 3 cm. in diameter. There is generally a diffuse pruritis with micropapules. The reactions vary in degree, 17.5 per cent being weak or negative, 72.5 moderate, and 1.4 strong. The results on the condition of the disease are given but the length of treatment at the time of assessing the results is not made clear. Of the 457 patients, 10 died of other causes, 19 became worse, 96 remained stationary, 334 improved, and of these last 259 improved markedly or very markedly. [This leaves a discrepancy of two.] It is concluded that, as in 79.9 per cent the state of the leprosy and the general condition [no mention is made of bacteriological results] improved, and in 56.4 per cent this improvement is of considerable degree, and as improvement is more rapid and stable (with fewer reactions) with the antigen than with the sulphones, " its efficacy is comparable to that of the sulphones, the action of which it simulates, and which it can replace advantageously."

The Histopathology of Acute Panniculitis Nodosa Leprosa (Erythema Nodosum Leprosum), by W. J. Pepler, R. Kooij and R. Marshall.

The authors consider the term " erythema nodosum " in leprosy to be misleading because their histological examinations of 20 specimens from 19 cases show a condition different from

what is generally described under that term. They base their opinion chiefly on the findings in the subcutis rather than in the dermis, and particularly in the fat lobule. " In early cases the histological picture varies from that of small foci of acute inflammatory-cell infiltration or serious atrophy of fat and small foci of necrosis, to an extensive acute panniculitis with numerous areas of abscess formation." The septa between the fat lobules show much less extensive infiltrate. In contrast with this the classical erythema nodosum is characterised chiefly by changes in these septa, which are enlarged by fibrinous exudate with leucocytes and giant cells, and contain the so-called reticuloendothelial nodules of Miescher. The authors therefore prefer the name "*panniculitis nodosa leproma*" for the reactive condition which occurs in lepromatous leprosy. The histological appearances of the two conditions are illustrated in three photomicrographs.

Tuberculization and Reactivity to Lepromin. Association between Lepromin and Tuberculin Reactions in School Children in Cordova and Opon, Cebu, Phillippines, by R. S. Guinto, J. A. Doull and E. B. Mabalay.

This study aims at determining to what extent a positive lepromin reaction indicates resistance to leprosy. " To determine what actually occurs, field studies in endemic areas are required, designed to measure attack rates in groups of persons differing in response to lepromin but comparable in other respects."

In 544 children of between seven and nine years of age a study of association between reactions to tuberculin (first and second strength PPD) and early and late reaction to lepromin. With the first PPD strength 14 per cent were positive, and with the second 71.9. With the early lepromin reading 4.4 per cent were positive, and with the late 65.3. In only 24 children was there a 10 mm. or more early lepromin reaction, and all of these had typical late reactions. Of these 24 there were eight positive to the first strength PPD, and all were positive to the second. The occurrence and intensity of the Mitsuda (late) reaction were positively associated with those of the PPD reaction. This would tend to show that tuberculization of the population may have been responsible for concurrent acquirement of reactivity to lepromin.

There are, however, disagreements in both directions: 9.5 per cent negative to PPD (of second strength) were positive to Mitsuda, though in all but one of these the Mitsuda reaction was weak, which suggested that it might be well in correlating the two

reactions only to accept lepromin reactions stronger than 1+. On the other hand there were 16.2 per cent positive to PPD but negative to lepromin, and in 63.6 per cent of 88 children with this type of disagreement the reaction to tuberculin was 2+ or more.

The only explanation of these disagreements is that, if the tuberculization hypothesis is true, certain persons can develop tuberculoid lesions when acid-fast bacilli are injected into the skin, but have lost or never possessed hypersensitivity to tuberculin; while in others hypersensitivity is present but the power to localize the bacilli in the skin by forming a tubercle is absent.

The article ends with the statement that until cultures of *Myco. leprae* are available " little progress can be made in the fundamental chemical studies which are essential for the elucidation of the nature of the lepromin reaction."

Experimental Studies on Transmission of Human Leprosy to Monkeys, by Shang-Ho Lai.

He describes the histories of 18 Taiwan monkeys (*Macacus cyclopis*) which had been inoculated with leprosy nodule suspension, and/or implanted with pieces of human leproma subcutaneously. In seven of these, clinical signs developed in the form of nodules, chiefly at the site but also at a distance, swelling of lymph nodes, and flexion of fingers and toes. He makes no mention whether bacilli were found in the distant nodules, nodes or nerves. There are 12 illustrations.

R. S. Buker, writing on *The Value of Leprosy Villages in a Programme of Prevention*, advocates the formation of leprosy villages, where patients can cultivate their land, choose their own leaders, and, away from the abuse that they are accustomed to in their original homes, lead a happy and normal life. " This kind of relative isolation is satisfactory isolation. It has been impossible, to date, to locate a single case of leprosy which has developed because of contact with one of these village cases by a person who lived outside the village. There probably are such cases, but they certainly are rare." Another advantage claimed is that they are economical, when funds and public opinion are not ready for a more intensive type of work, costing less than a tenth of larger colonies. It is acknowledged that without proper supervision there is a tendency for people to come from a distance and thus increase the total leprosy population in an area. [In fact the degree and quality of supervision is the essential point. As has been found

in India and Africa, gathering together of leprosy patients in one area without adequate supervision tends to increase rather than to control the disease.]

NEWS

India's Five-Year Anti-leprosy Campaign

According to the *Indian Express,* Madras, 100 leprosy control centres are to be opened throughout the country under the second Five-Year Plan. There was also a proposal to spend about Rs. 1.5 crores under the Plan for giving financial assistance to private bodies doing work on T.B. and leprosy control.

In the Madras State there is a proposal to train 200 medical graduates in clinical work for the treatment of leprosy.

The Leprosy Sanatorium at Thirumani is to be upgraded into an all-India teaching and research institution at a total cost of Rs. 30 lakhs (about £230,000). The scheme will be pushed through as soon as a new director is appointed.

Under the Government of India's Central Scheme (including the Extended Scheme) which was included in the First Five-Year Plan, at a cost of Rs. 30 lakhs, four Treatment and Study Centres and 31 Subsidiary Centres have been allotted to the various States where leprosy is a problem.

The four Treatment and Study Centres are located in Madras, Madhya Pradesh, West Bengal and Uttar Pradesh. Out of the 31 Subsidiary Centres Bihar was allotted 8, Bombay 1, Orissa 2, Assam 1, Vindhya Pradesh 1, Saurashtra 1, Madras 2, Madhya Pradesh 4, Andhra 2, Uttar Pradesh 1, Hyderabad 2, Travancore-Cochin 4, Himachal Pradesh 1, and West Bengal 1.

In the Treatment and Study Centres, apart from giving treatment and necessary health education on the subject, a survey of the type and intensity of leprosy prevalent in the area will also be made by a special team and the results achieved evaluated. The necessary laboratory facilities will also be provided for such studies. It is also contemplated to undertake large-scale trials on the efficacy of B.C.G. vaccination as a prophylactic against leprosy. In the subsidiary Centres treatment will be given on a mass scale and Health education carried out.

Many Leprosy Control Centres have been established in the various States. The Central Government will meet the entire recurring expenditure of the centres for the first six months; two-thirds of the expenditure for the succeeding 12 months and 50 per cent for the remaining period. The centre will also bear the cost of transport vehicles and the more important laboratory equipment and the entire cost of B.C.G. vaccination (about Rs. 20,000) as this will be a purely research project. The State Government will bear the balance of the recurring expenditure during the years 1954-1955 and 1955-1956 and salaries of local staff, if appointed; and will provide the necessary accommodation for the location of the clinic, laboratory and office of the centre free of charge. They will also continue the operation of the centres after the financial help from the centres ceases. The cost of co-ordination work in connection with the scheme will be borne by the Central Government.

ABSTRACTS*

Four Examples of Familial Leprosy in which Children were affected before the Parents. Rev. Coloniale de Méd. et Chir, 1954, Oct. 15, V. 26, No. 228, 1'82-4. By **E. Montestruc.**

In the four cases described the children showed the disease approximately 1, 6, 3 and 5 years respectively before the parents. The types of disease in the four children were respectively lepromatous, indeterminate, tuberculoid and lepromatous, and of the adults indeterminate in the first and lepromatous in the other three. Three possible explanations of these unusual occurrences are discussed: the adults might have been infected by the children; the children might have been infected by the adults in whom the disease might have been present in an infectious but unrecognised form; parents and children might have been infected by an unknown third party. The author is in favour of the last of the three hypotheses. (He does not mention what efforts were made to discover the third party.)

The Plasma Proteins in Leprosy. Rev. " Fontilles," Valencia, 1954, July, V. 3, No. 6, 467-478, 9 charts. By **F. Contreras, S. Miguel, A. Rod'an, J. Guillen, J. Terencio** and **J. Tarabini.**

While considerable study of changes in blood cells has been made in pathological conditions, the study of the humoral parts of the blood has lagged behind because of its complexity. For the latter the co-operation of chemists and physicists with clinicians is necessary. In leprosy the changes in the plasma proteins are of great importance, and for study the electrophoretic method has been found the most convenient.

After recounting the various vital functions of the proteins the authors give in tabular form an analysis of the plasma proteins in 46 leprosy patients, comparing their percentage deviations with normal deviations. The results showed an increase of total proteins in 44.91 per cent., and a diminution in only 3 per cent. Albumin was diminished in 66.66 per cent, and increased in only 2.23 per cent. Globulin percentage changes were: *alpha* 1 increase 39.02, diminution 17.07; *alpha* 2 increase 69-76, diminution 9.30; *beta* increase 14.89, diminution 19.14; *gamma* increase 63.82, diminution

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4.25. During lepra reaction the proportion of globulins (chiefly *alpha* 2 and *gamma*) increased considerably, returning to normal at the end of reaction. When there are diffuse hepatic lesions *gamma* globulin increases most. In leprous conditions where there is a diminution of proteins the authors recommend the transfusion of blood and plasma, which they have found very efficacious.

The Chemotherapy of Rat Leprosy. J. Applied Bact., 1954, Oct., V. 17, No. 2, 181-4 (11 refs.). By **Betty Croshaw.**

After recounting various trials of drugs that have been made for their effects on *Myco. leprae murium* (see this *Bulletin*, 1954, V. 51, 944, 1168, 1258) the author discusses his own experiments. Five different methods of inoculation and treatment are described. A suspension of ground-up nodule containing acid-fast organisms was injected: (1) in developing chick embryo; (2) subcutaneously in rats; (3) intraperitoneally in rats; (4) subcutaneously in mice; (5) intraperitoneally in mice.

The following drugs were tested: Sulphetrone, DDS, TB1, TB3, PAS, INH(isoniazid), acetone *iso*-nicotinyl hydrazone. There were also controls without bacilli, and controls with dead bacilli.

Only isoniazid and *iso*-nicotinyl hydrazone had any marked effect. " The latter drug undoubtedly acts by virtue of its breakdown to INH as shown by paper strip chromatography." However, the effect of isoniazid against *Myco .leprae murium* infection in mice is not so great as in experimental *Myco. tuberculosis* infections. It is considered that the results of further clinical trials with isoniazid in human leprosy should be awaited before the final value of experimental *Myco. leprae murium* infections in selecting possible drugs can be assessed.

Lepromin prepared from Formolized Lymph Nodes. Rev. Ecuatoriana de Hig. y Med. Trop. Guayaquil., 1954, Jan.-June, V. 11, Nos. 1/2, 106-10. By **E. Blum Gutierrez.**

As the grosser forms of lepromatous leprosy have become more uncommon the author has found it increasingly difficult to obtain fresh leproma from which to prepare lepromin without causing mutilation of patients, especially as the prominent lesions are generally on the face. The same difficulty has also been experienced in other South American countries. In the pathological department of the Hygiene Institute in Guayaquil there were available lymph

nodes which had be inexcised from a child with lepromatous leprosy. and which were rich in acid-fast bacilli. As these nodes had been preserved for 2 years in formalin the author considered that their value for preparing lepromin would have been destroyed. But on preparing a suspension by the usual Mitsuda method and trying it out on leprous patients of all types he obtained results comparable with those expected with antigen from fresh leproma. The advantage of using formolized leproma is that small pieces of tissue can be collected as occasion permits, and then suitable quantities of antigen prepared as required. A note is added mentioning that in Brazil lepromin antigen prepared from tuberculoid lesions had been found useless.

Two New Cases of Infant Leprosy in Martinique. Bull. Soc. Path. Exot, 1954, V. 47, No. 6, 781-3. By **E. Montestruc** and **R. Berdonneau.**

Two former instances of leprosy in infants were published by Montestruc (see this *Bulletin*, V. 51, 803).

The first of the two children in the present instance had an achromic macule surrounding the umbilicus at the beginning of its third week. At the time of examination when the child was 17 months old there were similar patches on the face and other parts of the body. Isolated acid-fast bacilli were found in serum taken from the chin. The source of infection had not yet been traced.

The second child was two months old when seen. From the third week of life there were numerous macules on the face. Bacteriological examination showed fairly numerous acid-fast bacilli.

The appearance of these very early cases of leprosy is considered as a sign of the tenacity and virulence of the local leprosy endemicity.

Perspectives in Pathology of Leprosy. Indian J. Med. Sci., 1955, V. 9, Suppl. 1, 44 pp., 27 figs. (22 coloured) on 10 pls. (75 refs.). By **V. R. Khanolkar.**

This is a series of four lectures which the author delivered in various countries, and which it was suggested " deserved publication, as they embodied some unorthodox ideas." The first gives the history of the pathology of leprosy from the time of Danielssen and Boeck up to the present time. The second deals with leprous reaction and the concentration of bacilli in skin biopsies, with

special reference to children born in leprosy homes and in highly endemic areas.

The third lecture deals with the nature and distribution of cutaneous nerves, and the changes which take place in them in the various types of leprosy. The question of nerve trunks as pathways for infection is discussed. The quotation from Payling Wright that " the semi-solid, or at least highly viscous, consistence of the (axonal) protoplasm discourages any belief that foreign material can be carried for long distances in relatively short times by streaming or circulation of the axoplasm " is contested by the author's statement: " We have recently been fortunate in obtaining transverse sections of fine cutaneous nerve twigs with the bacilli lying in situ and cut transversely. A study of these sections leaves no doubt in one's mind that bacilli are located and travel within the axons. This is illustrated in a few of the 27 illustrations which accompany the lectures. The last lecture describes the classification of leprosy and the changes which may take place in types.

Is the Rendering Positive of the Mitsuda Test by a Primary Tuberculous Infection accompanied by a Relative Anti-Leprosy Immunity? Bull. Soc. Path. Exot., 1954, V. 47, No. 6, 771-5. By **H. Floch.**

It has been noticed that in French Guiana the form of leprosy among the Europeans is more of the severe lepromatous type than among the indigenous Creoles. Comparing Creole with European prisoners, who come to French Guiana in adult life, it was found that among the lepromin-positive patients of the Creole group 73 were tuberculin positive as compared with 100 per cent in the European group; whereas among the lepromin-negative (chiefly lepromatous) patients the Creoles showed 40 per cent tuberculin positive as compared with only 33 tuberculin positive among the Europeans. This is accounted for by the fact that the Creoles had acquired some slight resistance to leprosy by contact with it during their earlier years, while among the Europeans such contact had not been possible. From this it is argued in reverse that a negative tuberculin reaction augurs worse for a European than for a Creole as he is more likely to acquire the negative lepromin (chiefly severe lepromatous) form of leprosy. It is further argued that a previous mild infection with tuberculosis gives para-immunity to leprosy, and that BCG vaccination gives a certain amount of resistance to leprosy.

Ocular Leprosy, with reference to certain cases shown. Proc. Roy. Soc. Med., 1955, Feb., V. 48, No. 2, 108-12 (Sect. Ophthalm. 2-6). By **P. D. Choyce.**

This lecture is part of a symposium at which ocular leprosy was discussed and six cases of leprosy of the eye were demonstrated.

The results of involvement of the VII and of the V nerves are described, the former causing myo-atrophy of the superior part of the orbicularis óculi muscle, and the latter causing corneal anaesthesia and sometimes ulceration of the cornea. Various theories of the modes of infection of the eyeball are discussed, the author favouring the opinion that " in view of the known predilection of the leprosy bacillus for peripheral nervous tissue . . . (it is a reasonable) theory that they migrate to these regions along the ciliary nerves." The pannus of leprosy is distinguished from that of trachoma by the absence of involvement of the tarsal plates, abundant anastomoses between the vessels, and a lesser degree of infiltration of the substantia propria. A statement is made that " secondary glaucoma is frequent and of great danger to the patient, as it is this complication which is, in part, responsible for the high incidence of blindness in ocular leprosy."

The claims of Elliott (this *Bulletin,* 1951, V. 48, 75) to have diagnosed six cases of leprous choroidoretinal lesions is questioned, leprosy being considered as confined to the anterior segment. Provided the disease is in the quiescent phase, ocular leprosy responds surprisingly well to surgical procedures.