G 30 320 or B 663—Lampren (Geigy)*

A Working Party held at the Royal Garden Hotel
London, September 1968

Chairman
Dr. M. F. R. Waters

Dr. R. H. Gosling (Geigy, Macclesfield) welcomed the participants and introduced the Chairman

1. ANTIBACTERIAL ACTION OF G 30 320 IN LEPROMATOUS LEPROSY
Effect on untreated lepromatous patients, with particular reference to bacteriology, considering the morphological index and then the bacterial index

MORPHOLOGICAL INDEX (M.I.)

CHAIRMAN: The morphology of *Mycobacterium leprae* is a controversial subject. Many leprologists believe, and I admit to being one of them, that fragmented bacilli are dead and that the majority of solid-staining bacilli are alive. Others remain unconvinced. Be that as it may, it is undisputed that leprosy bacilli become fragmented under effective anti-leprosy treatment. It was noticed from the first introduction of effective chemotherapy, and reported in 1946 by some of the giants of leprology (such as the late President of the International Leprosy Association, Dr. Fernandez, and our honorary Vice-President, Dr. Muir), that bacilli of patients under sulphone treatment soon become fragmented; and this fact was mentioned in the report of the Panel on Therapy at the 1948 Congress in Havana.

I now ask for your experience with the morphological index, which is defined as the percentage of solid-staining bacilli smears being taken at one time from several sites, and an average calculated. Before beginning, I would particularly like to welcome Dr. Vincent Barry, who discovered G 30 320 in his laboratories in Dublin, and Dr. Stanley Browne, who was the first person to use it clinically in leprosy. It seems appropriate to call on Dr. Browne to make the first contribution.

DR. S. G. BROWNE (LONDON): For many years we have used the morphological index (M.I.) as the most sensitive indication of the mycobactericidal activity of a drug. In early work with G 30 320 we habitually used the index as calculated from 8 body sites (including 2 from the septal mucosa of the nose), examined and stained by a uniform technique and dealt with by the same very experienced technician. Definite solid-staining and deeply staining bacillary forms were counted as normal; all other recognizable bacillary forms not deeply or uniformly staining were regarded as abnormal. The patients were all untreated. The average initial height of the morphological index was 54%, which may seem somewhat high to workers in other countries, but in the deeply-pigmented African with a very high turnover of epithelium and of nasal mucosal epithelium, this is not an unusual figure. The range was from 0 to 100, but in the great majority of patients the index would fall between 30 and 60%. In untreated patients with severe lepromatous leprosy under G 30 320 therapy, the index fell to zero in an average period of 30 to 32 weeks. The fall was regular, and occurred at all sites, but was sometimes less rapid in the nose than elsewhere. The rate of fall in pure lepromatous disease did not depend

*Editorial note: Some speakers referred to G 30 320 and others to B 663; for the sake of uniformity G 30 320 is used in this report. The chemical formula and structure of Lampren are given on page 47.
upon the initial height of the morphological index, or on the dose level of G 30 320 given. There was a transient rise in the M.I. from time to time of no prognostic significance; it occurred at one, at several sites, or at all sites, especially in the nasal mucosa. The bacilli were still sensitive to the drug, bacteriological progress being resumed on continued therapy.

There is no real difference between a dapsone regime and G 30 320 as regards the time taken to render lepromatous patients non-contagious.

**DR. J. H. S. PETTIT (KUALA LUMPUR, MALAYSIA):** I do not have much to add to the papers that are summarized in our book of abstracts.* As far as the morphological index is concerned, the fall is exactly comparable in sulphone-resistant and ordinary cases. You will see that it is steep at first, then much slower, and that the transient rise mentioned by Dr. Browne also appears in one or two of our cases. We do not use nasal smears at Sungei Buloh; all our smears are taken from other parts of the skin, but even then there is an occasional rise, as seen in 2 of the cases between the third and the sixth months.

**DR. J. M. H. PEARSON (SUNGEI BULOH, MALAYA):** The curves in Fig. 1 are averages for 4 different groups of 6 to 10 patients each, and the fall in the M.I. was plotted from smears taken every 6 weeks during the initial 6 months of treatment. Line A represents 6 cases on G 30 320, 100 mg twice weekly. Line B represents 100 mg daily. That was in a group of patients resistant to dapsone treatment. Lines C and D represent patients treated with G 30 320, 100 mg 3 times a day; one group is of previously untreated lepromatous cases, the other of cases with proved sulphone resistance. Line E represents the fall in a group of patients treated with dapsone, 50 mg twice weekly. This confirms what Dr. Browne said, that judged by fall in the M.I., patients on G 30 320 in the dosage we have used respond comparably to those treated with dapsone.

*The abstracts were available only at the meeting. A list of published reports on Lampren is available on request from the Geigy Company.

**DR. F. M. J. H. IMKAMP (KABWE, ZAMBIA):** I have a few patients in a drug trial who were corticosteroid-dependent for some years; their M.I. was still high and they responded to G 30 320 treatment, and the M.I. came down. One lepromatous patient was given a loading dose of 300 mg for 3 weeks and then 100 mg a week; his M.I. responded very favourably.

**DR. B. L. LEIKER (AMSTERDAM):** I have treated 42 patients, but all had received previous treatment. I have divided this group up into: (1) uncomplicated cases; (2) cases with previous serious reactions. We assessed bacteriological progress on serial biopsies taken every 3 months from the same lesion. Reduction of infiltration in the first 9 months of treatment is not marked. Some of these patients have been treated now for up to 2½ years, and in the second year of treatment the changes become more marked. Bacteriological progress is of the same order as with dapsone. The bacillary index decreased in patients on average at a rate comparable with that in standard dapsone treatment—a decrease of about one unit per annum.
CHAIRMAN: It is generally accepted that determination of a morphological index on bacilli in sections is more difficult than in smears, and I am very interested to see your results.

DR. B. L. LEIKER (AMSTERDAM): I found that the changes in smears were comparable with those in sections.

CHAIRMAN: I should point out that figures for the M.I. and the methods of assessing a solid-staining bacillus differ in different parts of the world. I understand that a W.H.O. working party will be discussing this very point after the Congress. However, even if the figures differ we can compare the shape of curves.

I want to show one curve (to be published) obtained from 8 histologically proven lepromatous cases who were previously untreated and had no dapsone in their urine. These patients received 100 mg G 30 320 twice a week, a much smaller dosage than that given to the majority of patients whose M.I. curves you have seen. Exactly the same shape of curve is obtained and, after 4½ months' treatment, very few solid-staining bacilli are left in the smears.

The evidence presented here shows that the M.I. falls rapidly in untreated lepromatous cases so that within a few months of the start of treatment there are very few solid-staining bacilli left. The rate of fall is comparable to that obtained with standard sulphone treatment, although no controlled comparisons have been presented this afternoon. That is my one criticism of this work.

BACTERIAL INDEX (B.I.)

Bacteriological index (B.I.) of Myco. leprae (Ridley's logarithmic scale)

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>1 bacillus in every 100 microscope fields</td>
</tr>
<tr>
<td>2+</td>
<td>1 bacillus in every 10 microscope fields</td>
</tr>
<tr>
<td>3+</td>
<td>1 bacillus in every microscope field</td>
</tr>
<tr>
<td>4+</td>
<td>10 bacilli in every microscope field</td>
</tr>
<tr>
<td>5+</td>
<td>100 bacilli in every microscope field</td>
</tr>
<tr>
<td>6+</td>
<td>1000 bacilli in every microscope field</td>
</tr>
</tbody>
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The B.I. is calculated from the examination of 6 to 8 stained smears under the +100 oil immersion objective.

CHAIRMAN: The bacterial index is the old standard method for assessing bacterial improvement. However, some prefer the 0 to 4 plus system, while others use Ridley's logarithmic index (0 to 6 plus). I would ask contributors to state which system they used.

DR. S. G. BROWNE: Our definition of the B.I. is the arithmetical average of the collated indices from a standard number of sites (8), the smears being taken by a standard technique. We have used the old Dharmendra notation from 0 to 4, which is roughly geometrical and roughly comparable to Ridley's 0 to 6. The rate of fall in untreated patients with lepromatous leprosy varied tremendously. Some patients, especially those with long-standing lepromatous disease, seem unable easily to get rid of acid-fast material from their skin and nasal mucosa. The index varies also with the amount of acid-fast material there is to be removed, that is to say, with the actual bulk of the subcutaneous granuloma. The average rate of fall of the B.I. in one series was up to 34% in 6 months, 46% in 12 months. There was no apparent relation between the high doses given in one series, 300 mg/day, and the lower doses of 100 mg/day or 100 mg every other day given in another. Nor was there any significant difference between patients who had a loading dose of 300 mg/day for 3 weeks followed by a standard dose of 100 mg/day, and others who had no loading dose.

Can the B.I. be reduced by increasing the dose of G 30 320? It is possible, but in my opinion very unlikely, because the mechanisms of killing mycobacteria are different from those for removal of effete acid-fast material from the tissue. Bacilli-filled macrophages must still be induced to leave the sites where they are congregated. We have experience of some examples of transient rises in the B.I.; various explanations are given, such as the vagaries of smear-taking, the existence of small pockets of morphologically normal bacilli, semi-encapsulated material in fibrous tissue, and the sudden recrudescence of bacillary activity in a localized area. The hormonal disturbances of parturition and pregnancy may also account for a transient non-significant rise in the B.I.
DR. R. C. HASTINGS (CARVILLE, LOUISIANA): Our experience has roughly corresponded with Dr. Browne’s. The B.I. as determined from skin scrapings falls quite adequately with G 30 320.

DR. GRACE WARREN (HONG KONG): I have been using G 30 320 mainly in the treatment of Chinese patients with chronic lepra reaction. This is usually long-term erythema nodosum leprosum (ENL), with high fever, arthritis, neuritis and iritis. To these patients we gave G 30 320, in most cases after every other available anti-leprosy drug and many other treatments had been tried, including prednisolone in some cases.

The first patient to whom we gave G 30 320 was a girl (No. 1486) who had been bed-ridden for almost 12 months, and whose bacteriological index had made no progress for 4 years. A number of sulphones were tried, and at the end of 1966 sulphoxone was given, then stopped and G 30 320 started. 300 mg/week was continued for 6 months during which time her B.I. fell from 3.8 to 2.3. She still continued to have some lepra reaction until we increased the dose to 600 mg/week, which controlled it completely. The B.I. has continued to fall through at a slightly slower rate, but compared with her previous state this is a very dramatic fall.

By the time that a further supply of G 30 320 arrived, we had many patients asking for the new drug. In a male patient (No. 1340) who started on G 30 320 in the middle of 1967, the B.I. fell continued at about the same rate that we had been achieving with injected thiambutosine, but his general condition improved dramatically. Another patient (No. 1661) had chronic reaction for 2 years with no improvement in the B.I. Once she commenced G 30 320, the B.I. fell dramatically; reaction was controlled by 600 mg/week, though not by 300 mg.

Another patient (No. 1447) had made slow progress over a period of 6 years. On G 30 320, the fall in B.I. was very dramatic for the first 6 months, but then stopped despite continued therapy. We have seen this in a number of patients, but have no explanation for it yet. The reverse may be seen (No. 1333). For the first 6 months on G 30 320, the general condition may improve without the B.I. showing any improvement; then there may be a rapid fall. The dose needed to control reaction has varied from one patient to another. There seems to be some relation between the rate of B.I. fall and the amount of drug given, but I have not been able to determine it properly yet.

CHAIRMAN: You recently published a paper on the rate of B.I. fall in patients on standard sulphone treatment. How does this compare with the fall on G 30 320?

DR. WARREN: The standard rate of fall of B.I. in Chinese patients on dapsone therapy is 1 unit/annum. It falls in annual steps from 4 to 3 to 2 to 1. After that you cannot predict how Chinese patients will react. The fall in B.I. in patients on G 30 320 was, in the 12 months under consideration, usually equal to or greater than the fall expected in patients receiving dapsone. In most cases, the fall was much greater than that for the same patient in the previous control period.

CHAIRMAN: Having many Chinese patients myself, I quite agree that it is difficult to predict the B.I. fall in the lower range.

DR. E. F. SCHULZ (PRETORIA, SOUTH AFRICA): Although we have not treated any patients with G 30 320 alone, and all our patients had dapsone before we started the trial, we attempted to establish whether the addition of G 30 320 to dapsone could increase the rate of fall in the bacteriological index.

We have had 2 groups of patients: one on dapsone alone, and the other on 100 mg G 30 320 daily plus dapsone. After 18 months there was no difference in the bacteriological index between these 2 groups. There was a marked difference in the incidence in reactions, but that can be discussed later.

DR. A. KARAT (KARIGIRI, INDIA): I would like to ask 3 questions. One is to Dr. Browne. He stated that in 12 months he expects a bacterial clearance of 34 to 46%. This is very unusual in our experience. We use Ridley’s scale, and make smears from 8 sites. Second, I noticed in the previous discussion that both he and Dr. Pettit emphasized a transient rise of morphological index. Was there any change in the B.I. at this
time? Was there any clinically recognizable change in the lesion when the morphological index went up? Third, in our experience, the rate of clearance of bacilli in lepromatous patients is somewhat proportionate to the initial bacterial index—the higher the initial index, the greater the drop in the first 12 to 24 months. In other words, whereas I normally expect a change in Ridley’s index of 1/year, just as Dr. Warren has described, clearance is quicker in those with a larger number of bacilli until they attain between 2 and 3.

DR. BROWNE: I agree that by south-east Indian standards, these figures may seem unusual. On Dharmendra’s notation, the fall was from between 4 and 3.5 to between 3 and 2.8, which would be reflected by a slightly different rate on Ridley’s scale. There was no change in the clinical condition suggestive of an increase in the morphological index at the time that this occurred, except that from time to time small cutaneous papillary elevations appeared, replete with morphologically normal bacilli, confirmed histologically and apparently arising in an umbrella-shaped fashion from a focus in the cuticular nerve tissue. The higher the original index, the greater the rate of fall initially under G 30 320, under dapsone or any other therapy. I believe that this finding may be more marked the further east one goes from central Africa.

DR. J. PETTIT: The transient M.I. rise found in some cases is not important. It is not reflected in the B.I., because the M.I. rise usually takes place about the third to fifth month, when there has not been enough time for a significant change in a B.I. with a logarithmic index.

PROF. GATTI (BUENOS AIRES): As far as the B.I. is concerned, my experience is that the fall during treatment with G 30 320 is comparable with that on dapsone, and more rapid than with long-acting sulphonamides or thiambutosine.

DR. RODRIGUEZ (MEXICO): In Mexico many untreated patients show a fall in the M.I. and this should be borne in mind when considering the effect of drug treatment.

DR. BROWNE: My early figures were based upon several series in Nigeria. We have some patients on G 30 320 today in this country whose B.I. has shown practically no change after 6, 9 and even 12 months. We are up against the problem of getting rid of unpalatable mycobacterial debris, and this apparently is not affected by any drug at present given for leprosy.

We also have noted variations in the M.I. in patients not under treatment, and therefore advocate the taking of fortnightly smears on at least 3 occasions before the beginning of any controlled therapy. When a patient is admitted to a leprosy settlement, the regular life, the good diet, and the restful atmosphere may all contribute in some unexplained way to a change in the M.I. I would, in contrast to Dr. Leiker’s proposal for a 3-monthly assessment of such indices on biopsy findings, advocate a monthly assessment from 8 sites. In that way much better understanding of the average bacteriological activity in skin and nasal mucosa would be obtained.

DR. PEARSON: Fig. 2 shows average changes in the B.I. (Ridley’s scale) in patients who had
previously been untreated or who were sulphone resistant, and therefore at the time of starting treatment with G 30 320 were in effect untreated. The figures on the curve represent the number of patients included on each occasion. The rates of fall appear to be different on different doses of G 30 320, but the number of cases is small and it is possible that there are no significant differences. The rates of fall appear to be comparable with those found during routine sulphone treatment.

DR. KARAT: I wish to underline what Dr. Browne has said. We have done some work on twice-monthly morphological indices, but for some unexplained reason they fluctuate significantly even when patients are not on any specific treatment, and I think the point is well taken. In our experience the clearance of bacilli is in some measure related to the dose of dapsone in lepromatous leprosy patients.

CHAIRMAN: We have had clear evidence that the B.I. does fall under G 30 320 treatment. I gain the impression that speakers who discussed B.I.’s from previously untreated patients receiving G 30 320 as their first drug reported a rate of fall comparable to that obtained with dapsone, although again no fully controlled trials were presented. The B.I. charts from Dr. Warren’s patients who had previously received a number of different drugs and whose bacterial indices had become stationary showed a very definite fall.

CONTROLLED TRIALS

CHAIRMAN: If anybody has any provisional results from a controlled trial, I should be most grateful if they could be presented now.

DR. KARAT: I think the terms “controlled trials” and “preliminary results” with G 30 320 are open to criticism for the following reason. In our group at the end of 30 days the trial ceased to be “controlled” if the patients were receiving 600 mg or more of G 30 320/week, and therefore the results I gave are classified as “controlled”, but in fact after one month they have become “randomized” trials rather than “controlled” trials. With that proviso, I would add that among the 17 patients we have been following up for the last few months, the changes in the 2 groups receiving 600 mg G 30 320 and 600 mg dapsone are identical.

DR. RUSSELL (NEW GUINEA): We began to study G 30 320 at a leprosarium in New Guinea and attempted controlled trials. We were defeated because the rate of admission of completely untreated new patients was too slow for us to select adequate numbers. We also ran into difficulties of fair and honest matching of patients to put into these 2 control groups. We have treated in all 31 patients, starting with 7 on dapsone and 7 on G 30 320 alone. We determined the bacteriological index (Ridley) using a series of 6 smears, including nasal. Two of our patients on dapsone very rapidly became negative and the rate of fall was in fact more rapid than with G 30 320.

After an average of 20 months’ treatment, we had 4 completely negative smears, which compares with similar claims for the M.I. With the sulphones in the same period (of roughly 20 months) we found 2 negative smears out of 7. In the first 3 months we observed a transient rise in index in the smears of several patients; then gradually the smears began to alter.

We have now abandoned any attempt at a controlled trial and are treating a greater number of patients in chronic reaction—comparable with Dr. Warren’s—who have had a series of drugs, including very long periods on steroids. We have tried to concentrate help on this type of problem patient. In some institutions 30% of our patients are in reaction. Lepra reaction improved in 16 patients without any doubt. We had 11 failures, but some of these responded later. We are still pursuing this.

CHAIRMAN: This report illustrates the difficulties of performing controlled clinical trials in leprosy. I wonder if Dr. Leiker has any information on controlled trials.

DR. LEIKER: Yes, we have a series of comparable data, but not matched pairs of patients. In a reliable control group the results were practically the same as with G 30 320.
HISTOLOGY

PROF. GATTI: After 6 months' treatment with G 30 320, there was a decrease of acid-fast material and fewer Virchow cells in both borderline and lepromatous cases, with some increased fibrosis and mild pigmentation in the basal layer of the skin in lepromatous cases. In one indeterminate case the neuritic infiltrate practically disappeared in 6 months.

DR. R. C. HASTINGS: We have used G 30 320 in various combinations on 9 patients for from 12 to about 38 months. We compared the Ridley biopsy index in 3 groups, each of 3 patients, on G 30 320 plus INH (isoniazid), G 30 320 alone, and G 30 320 plus dapsone. Among our patients 2 are sulphone resistant (one confirmed in the mouse foot-pad) and 5 had been treated for chronic erythema nodosum leprosum. We expressed the biopsy index as a percentage of the pre-treatment value.

We were a little disappointed in the combination of G 30 320 (200 mg daily) and INH (300 mg daily). After some 30 months, the index was 63% of the original biopsy index. With G 30 320 alone, the index fell to about 50% of the its pre-treatment value. We compared results with the recorded values of a 25 to 30% drop every 6 months in the biopsy index reported for sulphones and our results did not seem to be quite as good.

CHAIRMAN: There are 2 aspects to histological studies. One is the histological changes under treatment, and the other the assessment of the biopsy index, and its rate of fall under treatment. I should like to confine discussion to the rate of change or rate of fall of the biopsy index.

DR. J. PETTIT: I have little to add to the published statements. The fall in biopsy index in a series of 6 cases of lepromatous leprosy (2 borderline) was 40% in a 5-month period, the assessments being made according to the biopsy index as amended by Dr. Ridley.

PROF. GATTI: The biopsy index has been studied in 13 patients and we obtained results similar to those of Dr. Pettit, the fall being 37% in 6 months.

DR. N. C. DA SILVA (RIO DE JANEIRO): I would like to emphasize the importance of histological and histochemical findings in drug trials. We have developed a technique based on differential staining for lipids with a yellow dye which we prepared from the pollen of dahlias. After treatment with G 30 320 there was no specific staining of lipid, but a diffuse penetration of the epithelioid cells in tuberculoid lesions. In lepromatous cases there was also diffuse penetration of lepra cells and epithelial cells with the stain; the section took on a golden tone and we saw some orange crystals which sometimes fluoresced.

PROF. E. AZULAY (RIO DE JANEIRO): We published a paper about 15 years ago on the effect of dapsone on the histopathology of lepromatous leprosy. At that time we did not have the bacteriological or morphological indices, but we observed Virchow cells completely devoid of all bacilli after 3 to 4 years of dapsone treatment. The infiltrates were less marked but we sometimes found 2, 3 or 4 Virchow cells still present without any bacilli at all. In my opinion the Virchow cell is the last to disappear, at least with dapsone treatment.

CHAIRMAN: We have had only a small number of contributions on histology, but by reference to published papers and so on, we know that G 30 320 does cause a fall in the biopsy index. On the short term and in non-controlled trials, this rate of fall seems to be somewhat similar to that with dapsone.

CLINICAL RESULTS

CHAIRMAN: We will now discuss clinical appearances and the influence of G 30 320 on leprosy lesions at different sites, again restricting ourselves to previously untreated lepromatous patients. We start with skin lesions and then deal with other structures, such as nerves, eyes and viscera.

DR. BROWNE: In the various forms of untreated lepromatous leprosy characterized by pre-lepromatous macules, lepromatous macules, nodules, or diffuse infiltration, there is a marked regression of all lesions, including re-pigmentation of the hypopigmented pre-lepromatous and
lepromatous macules, and flattening of the raised lesions—papules, nodules, plaques and diffuse papular infiltration. The hyperpigmentation in these lesions is extremely variable, not only in deeply pigmented but also in lightly pigmented Caucasian skin. In some patients the difference in pigmentation (ruddiness and hyperpigmentation) is scarcely noticeable, even though 100 mg/day of the drug is given. In others 50 mg/day will produce a most noticeable ruddiness followed by slatey-grey hyperpigmentation.

To particularize on the raised lesions of leprosy, the small highly bacilliferous papules tend to flatten rapidly, losing their pinkish and yellowish coloration and gradually merging into the surrounding, apparently normal skin. They leave small scars, shiny and lightly striated, frequently hyperpigmented for several months while treatment with G 30 320 is continuing and even after it has stopped.

The flattening of nodules on ear lobes and at other sites of predilection on the face proceeds more slowly, depending upon the depth of granulomatous tissue to be acted upon by the drug and on the fibrosis following its specific mycobactericidal action. In other words, the nodules take much longer to flatten than do the highly bacilliferous and oedematous papillary elevations in the skin. When the nodules do flatten and disappear, their place is taken by puckered scars, the degree of puckering depending upon the initial depth of the granulomatous infiltration of the dermis. The plaques and larger areas will repigment and may even hyperpigment, often after a localizing of the ruddiness which is apparent in variable degree. The larger papillary areas may take a long time to flatten; in other words, where there has been a high initial degree of infiltration in the dermis, the fibrosis is a slow continuing process not greatly accelerated by G 30 320 or by any other anti-leprosy drug.

In previously treated lepromatous leprosy patients with a high degree of dermal fibrosis, absorption of the granuloma is very slow and may take several years; during that time the hyperpigmentation due to G 30 320 will persist. This may be socially unacceptable to groups of patients with lightly-hued Caucasian skin, but those who have been treated for persistent exacerbation regard it a small price to pay for steady amelioration of their clinical condition and a general sense of well-being.

PROF. GATTI: I would confirm what Dr. Browne has just said. There is a flattening of lesions beginning between the first and the third month of G 30 320 treatment. The lesions become less infiltrated and then pigmented. The nodules are flattened, atrophic and wrinkled. All this is more evident at the sixth month.

DR. J. TOLENTINO (CEBU CITY, PHILIPPINES): I should like to tell you about a patient with very advanced lepromatous leprosy, who had huge lepromatous nodules all over the body and had been receiving dapsone for a long time, but steadily deteriorated. He was then given thiambutosine without any improvement. Finally, G 30 320 was tried, and the improvement was very remarkable, so much so that in one year about half the nodules had subsided and many of them became flat.

CHAIRMAN: This was a patient with presumed sulphone resistance.

DR. IMKAMP: One of my patients with lepromatous leprosy was thiambutosine resistant. After about 12 months' treatment with the injectable form, the M.I. actually rose; she was also prone to ENL. After G 30 320 was started, she had one mild ENL reaction, which responded to an increase in dosage. The M.I. is now zero. The disease is clinically inactive, and she is employed on the wards.

DR. SCHULZ: I have treated a patient for 18 months with a combination of G 30 320 and dapsone, one of a controlled group of 16 patients, with 15 patients on dapsone alone. He had diffuse lepromatous leprosy, with nodules; after one year the marked flattening of the nodules and the pigmentation are well seen. I cite this case to plead for controlled trials. This patient did remarkably well. After 18 months there was no significant difference in the improvement in the clinical appearance of the 2 groups.
CHAIRMAN: I fully support your plea for controlled trials. As, in particular, the huge trials by the Leonard Wood Memorial group in the early 1950's showed us, the only way to assess any drug accurately is by a controlled clinical trial.

DR. E. KARURU (FIJI): I have observed the return of sweating in tuberculoid and some other types of leprosy after treating with G 30 320.

Ocular Effects

DR. GRACE WARREN: Of the 48 patients that we have treated with G 30 320 so far, about 35 had previously had eye complications, mostly iritis. Most of them had no recurrence of iritis after 3 or 4 months on G 30 320. At the beginning, since I was not checking the eyes regularly, the condition may have come under control sooner, but there was only one patient—a girl who had been on prednisolone—whose eye lesions remained active for about 6 months. In the others, the iritis was brought completely under control within 3 or 4 months of commencing G 30 320.

DR. IMKAMP: All our patients on G 30 320 were examined with the slit lamp by an experienced ophthalmologist, and no active ocular disease or abnormal pigmentation was found.

DR. HASTINGS: Dr. Margaret Brand has examined my patients periodically with the slit lamp, and there seems to be general improvement in both the bacteriological and the reactional states in the eyes. There may be circumcorneal pigmentation which mimics an iritis on superficial examination.

DR. BROWNE: I should like to emphasize the deposition of micro-crystals in the cornea, particularly in the meridional region in the African Bantu, who is subject to various lesions in that region; this finding is of no prognostic significance and there is no disturbance of ocular function. I would confirm the improvement in acute iritis and iridocyclitis during administration of G 30 320 and the general amelioration in the patient’s condition as showing the activity of the drug. It has a non-specific effect in reducing the duration and severity of acute iritis.

Visceral Changes

DR. KARAT: We find that in patients in reaction any lymphadenopathy tends to regress after between 10 and 14 weeks when they are given doses of 300 mg G 30 320 daily. Second, for some unexplained reason, red cells appear in the urine between the fourth and the eighth week, and tend to disappear between the twelfth and eighteenth weeks. We have studied a few renal biopsies, but the findings are preliminary and we cannot yet discuss them. Third, there has been a change in creatinine clearance in patients on G 30 320 as compared with those on prednisolone. Fourth, the improvement in blood findings over a period of 4 months has not been impressive, though the changes in albumin levels are somewhat encouraging. Lastly, I was very impressed by the subsidence of unexplained bilateral pitting oedema both in untreated lepromatous leprosy and in the reacting group, while the patients were having G 30 320. I infer that this may have something to do with the alteration in creatinine clearance that I have already referred to.

PROF. GATTI: I should like to mention the lesions seen in the mucosa of the throat and larynx. These include ulcerative lesions in the throat, including the uvula and tonsils, and congestion. After 6 months' treatment with G 30 320, intense fibrosis of the lesions could be seen and the ulcers disappeared. One patient complained of dyspnoea and fatigue, and thought he had asthma. He was treated with 300 mg G 30 320/day, and the dose was later raised to 600 mg/day. Examination by a throat specialist at the sixth week confirmed increased fibrosis in the resolving laryngeal lepromas. The fibrosis aggravated dyspnoea and necessitated the addition of corticosteroids to his treatment. Recently he had a fatal attack of acute respiratory obstruction which appeared to be due to mucoid secretion, not to the medication he was receiving.
DR. GRACE WARREN: All our patients have had liver function tests done regularly every 3 months for 12 months. As all these patients were in reaction, the majority showed definite signs of abnormality at first, particularly inversion of the albumin : globulin ratio, but this tended to revert to a normal pattern. Electrophoresis was carried out on all these patients; in 6 months the electrophoretic patterns had returned to normal in the majority. Results of other tests tended to follow the same pattern.

DR. A. RENDERS (BRUSSELS): The accompanying colour plate (p. 35) shows the remarkable clinical improvement, especially in cutaneous lesions, typical of 4 of the 34 patients treated with G 30 320 at a Leprosarium in the Congo. In one patient with lepromatous leprosy there was considerable reduction in the elevation of the nodules after 18 months' treatment with this product. Another case of borderline leprosy showed a considerable clinical improvement after 18 months' treatment with G 30 320. Another patient who came to the Leprosarium, guaranteed non-treated, who after being treated for 3 months with a dose of 300 mg/day of G 30 320, left the leprosarium without permission. But even in 3 months there was remarkable improvement in this patient. A patient with obvious nodular lepromatous leprosy showed the difference after only 6 months' treatment with G 30 320.

Neurological Aspects

CHAIRMAN: That concludes all the straightforward clinical side apart from neurology, in conjunction with which there are several questions to be answered. In lepromatous leprosy, does sensation improve during treatment with G 30 320? Is there any relation between G 30 320 and nerve pain? How much does the drug help in established neuritis, and can it prevent or in any way affect the development of neuritis in previously untreated patients who receive G 30 320 as their first drug?

DR. KARURU: A part-Chinese, 37-year-old man, was admitted 2 years before receiving the drug: he had glove-and-stockling anaesthesia, was lepromin positive, and also had lepromatous nodules. He was diagnosed as dimorphous leprosy. After the eleventh month of treatment with G 30 320, he regained sensation in the upper part of the leg. Since I took no biopsy, I was unable to do a proper neurological study, but the fact remains that sensation returned.

PROF. GATT: We had 4 lepromatous patients with severe neuritic pains. Improvement was rapid after the second week of G 30 320 treatment, with disappearance of the pain.

DR. A. KARAT: We have studied changes in sensation over a period of 6 months, carefully mapping the areas in the upper and lower limbs every month. To date, in the 24 patients under observation, we find no change whatever in sensory modalities as compared with the beginning of the trial.

CHAIRMAN: How does this compare, say, with patients treated with dapsone?

DR. A. KARAT: The same.

DR. W. JOPLING (LONDON): Swelling and pain in peripheral nerves may be part of a lepra reaction in lepromatous leprosy, and is one of the aspects of the reaction which will respond to treatment with G 30 320. The important thing here, as in the management of other aspects of lepra reaction, is the dosage used. With a small dose such as 100 mg every other day, there might actually be a recrudescence of neuritis, but by increasing the dose according to need, the neuritis and other aspects of lepra reaction can be brought under control. I think this question of dosage according to patients' needs is one that must be considered very seriously.

DR. S. G. BROWNE: In early lepromatous disease, G 30 320 is valuable because it hastens clinical and bacteriological cure. In other words, the patient is cured before he gets to the stage of reversible or irreversible polyneuritis. There is, however, no evidence that G 30 320 is superior to dapsone or other anti-leprosy drugs in this respect. In early established neuritis with inflammation and oedema, the general clinical picture of acute exacerbation will
respond to G 30 320 and the polynervitis will improve, with concurrent improvement in the sensory and the motor modalities. That would be similarly reversible by other anti-leprosy drugs if they had a similar anti-inflammatory action. In established, fibrotic polynervitis there is little or no response. The most dramatic response is, of course, in acute inflammation with localized swelling and tenderness of the peripheral nerves at sites of predilection. As I reported some years ago, in these patients there is a substantial and rapid improvement in the pain and tenderness in the nerve trunks.

**Dr. B. Leiker (Holland):** In Holland, 5 borderline tuberculoid cases with marked nerve involvement, pain and swelling have been treated with G 30 320, 2 patients with 100 mg daily, one patient with 300 mg twice a week, and 2 patients with 100 mg every second day. All showed active, some reactive, skin lesions and I regard the administration of sulphones in these cases as most risky. I should prefer to start with steroids before giving sulphones. These 5 patients were treated with G 30 320, 2 of them initially receiving a moderate dosage of steroids. None has shown an exacerbation; pain and swelling subsided, in all, in 3 within 4 months, in one within 5 months and in the fifth patient within 6 months. The steroids given to 2 patients could be withdrawn after a few months.

**Dr. R. C. Hastings:** Every 6 months we usually do motor conduction velocities, with more frequent sensory examination and manual testing of motor power. In brief, we have seen no detectable trend in over 3 years' experience with G 30 320 although these parameters vary somewhat.

**Dr. F. Imkamp:** We found that in neuritis which was part of the ENL (erythema nodosum leprosum) pattern, the pain and also the swelling of the nerves responded to an increased dose of G 30 320 according to the individual needs of the patients. I cannot say anything about changes in sensitivity, as we were dealing with longstanding lepromatous cases which had been suffering from erythema nodosum for many years.

**Dr. Grace Warren:** I should like to agree with what Dr. Jopling said about the neuritis being part of the lepra reaction. In our cases we found that this was so. Regulation of the dose of G 30 320 would control lepra reaction, and it also controlled the neuritis. One particular patient (No. 1685) required 200 mg/day to control his reaction and neuritis, and after he had had no neuritis for 6 to 8 weeks complained one morning of neuritis. After careful questioning, which took 24 hours to extract the truth, he owned up that he had 12 capsules of G 30 320 in his locker which he had not taken. He went back on his full dose, was neuritis-free a fortnight later, and has stayed free. Whether it is coincidence or not I leave to the imagination, but it is the only recurrence of neuritis we have had in patients on G 30 320.

**Chairman:** Thank you, Dr. Warren. This brings up a very important point, which is that in all scientific work in leprosy you cannot completely trust the patient. It reminds me of that very honest and interesting paper, which was briefly reported in *Leprosy in India*, of a trial of Ayurvedic medicine in lepromatous leprosy. In this, about one-third of the patients improved, but it was found that those who improved had sulphone in the urine. I admire the author who published that account—it was a lesson to us all.

**Dr. A. Karat:** In the reaction group our findings are entirely in agreement with Dr. Jopling's. The results with 300 mg of G 30 320 daily are infinitely superior to those with 15 mg of prednisolone in the Grade 3 and 4-plus reactions. I am referring only to the acute painful neuritis that occurs concurrently with erythema nodosum. While conduction velocities, muscle function and sensation remain unchanged in both groups, the relief of pain was gratifying and significant.

**Dr. E. J. Schulz:** We have treated 13 patients with neuritis, 8 of them were part of our ENL group and 5 with neuritis alone. All improved and most cases were completely controlled. Some required up to 300 mg daily. Two relapsed after treatment was stopped.
2. **G 30 320 IN TUBERCULOID AND BORDERLINE LEPROSY**

CHAIRMAN: We shall move on to the value of G. 30 320 in tuberculoid, borderline and indeterminate leprosy. A number of speakers have already slipped in a few words about this.

DR. R. E. PFALZGRAFF (NIGERIA): For about 5 years I have been using steroids much more freely than most people recommend, primarily in patients with tuberculoid or dimorphous (near tuberculoid) leprosy. Steroids are most valuable in these patients. However, with G 30 320 we can begin to consider omitting steroids in such cases.

In one patient under treatment with dapsone, there were signs of slight reaction in his skin lesions, but more significantly he had large and painful nerves. In similar patients, I would have used steroids, but I decided to try 100 mg/day of G 30 320 and the result has been good, without steroids. The ulnar nerve in this patient was roughly 12 mm in diameter by caliper measurement, and quite painful. About 4 months later, the diameter was about 9 mm.

What has been said about lepromatous patients is completely true of tuberculoid patients, of whom we see many more. It looks as if G 30 320 will make a great difference in the treatment of the problem tuberculoid case.

PROF. J. GATTI: We had 3 tuberculoid patients free of skin lesions but with residual neuritis who were treated with 300 mg/day; there was an improvement after the second week of treatment, with disappearance of the ulnar pains and subjective sensations.

3. **G 30 320 IN SULPHONE-RESISTANT LEPROSY**

CHAIRMAN: We will move on to the value of G 30 320 in patients with sulphone resistant leprosy. This is a subject that has largely developed since the last international conference and, in particular, with the use of the Shepard foot-pad technique, giving laboratory proof of sulphone resistance that has been suspected clinically. A number of papers have been published on this subject and Dr. Tolentino has already told us about one patient with presumed sulphone resistance who responded very well indeed to G 30 320. I saw him just a few weeks after he started the drug, and was very happy with his progress even at that early stage.

DR. J. M. H. PEARSON: We have a series of between 20 and 30 patients with proved sulphone resistance and I have already shown the response in terms of fall in morphological index. Sulphone-resistant patients respond in just the same way as previously untreated patients. Clinically, over periods of up to 4 years, improvement has continued on gradually reducing doses of G 30 320. We have had no cases of G 30 320 resistance so far. Three patients treated for just over 4 years with G 30 320 have all responded satisfactorily. One who was strongly lepromatous has now become smear-negative in the skin. The others have been treated for periods of a few months to about 3 years.

DR. R. C. HASTINGS: We have only one patient with foot-pad proven sulphone resistance who has been on G 30 320 for about a year; he has responded quite well.

DR. S. G. BROWNE: We have 2 cases of foot-pad proven dapsone resistance, and 3 suspected cases. All—even those whose condition was complicated by severe exacerbation—have responded very satisfactorily to G 30 320 up to a period of 29 months, and no case of G 30 320 resistance has developed.

DR. D. LEIKER: We have no cases of proven drug resistance, but I regard cases that have been treated for 10 years with sulphones and have not improved bacteriologically in the last 3 to 4 years as most likely to be resistant. These, and patients with signs of exacerbation (or increases in the bacillary index, and in the number of intact bacilli) have responded very
well to 100 mg of G 30 320/day. Altogether, we have 14 patients now on treatment who have received G 30 320 for between 1 1/4 and 2 1/4 years. There is so far no evidence in the smears or the biopsies of resistance to G 30 320.

CHAIRMAN: The small numbers of lepromatous patients who relapse after 10 years or more of treatment, and develop active lepromatous leprosy again after, in some cases, going almost smear-negative, are becoming increasingly important. A number of workers, some of whom have spoken briefly just now, have written on this subject, and in particular they have recorded the value of G 30 320 in sulphone resistant patients. I have felt it my duty as Chairman to remain as impassive and as unenthusiastic as possible, but this is one subject on which I cannot hide my enthusiasm. These patients are cropping up increasingly. As I have travelled round different leprosaria, I have always been shown a few of them, and I think we will be finding them more and more over the next few years. As clinicians we must particularly look out for them.

DR. E. KARURU: One patient of particular interest to me was a Fijian male, aged 57 years, who was first admitted to Makongai in 1941 with lepromatous leprosy, and treated with chaulmoogra for 8 years with no change except that he started to develop dermatitis at the end of that period. When dapsone was introduced in 1949, he was considered suitable for trial. He developed skin reaction as soon as he was started on the drug. Several months later, he was again given sulphone, but the skin reaction was more severe and accompanied by marked oedema, so the treatment was stopped. He was then put on chaulmoogra for another year before starting him on amithiozone, which caused no ill-effects, and resulted in recovery 8 years later. He was discharged in 1958, but for some reason did not continue taking his tablets. He relapsed in 1963 and he was re-admitted to the hospital. On re-admission he showed lesions of the 2 polar types of leprosy and was classed as dimorphous. Thiacetazone was given again in larger doses than originally, but his condition became progressively worse. After 8 months it was evident that another drug had to be used. Thiambutosine was tried, but 6 months later he suffered nodular reactions and developed a right foot drop. The drug was discontinued, and prednisolone given to control the reaction. Amithiozone was tried again in small doses of 50 mg, slowly increasing to 100 mg/day. Five months later he developed dermatitis. The patient was found to be allergic to several drugs, even including the usual preparation of procaine. Before G 30 320 was tried, his B.I. was worse than before (deteriorating from 0 to 3.5), and the clinical condition was even more severe. After 2 months' treatment with G 30 320, his lesions were clearly receding, the nodules were flattening, and it became clear that this was the drug that we had been seeking. As one of the members of the staff said, "Thank God the drug is doing something for this poor fellow."

CHAIRMAN: Another problem is the patient resistant to one drug who cannot take sulphones because of sulphone allergy. Drs. Pettitt, Pearson and I have been studying a small number of patients with thiambutosine resistance, who also had sulphone allergy and could not take dapsone. In these patients, too, we found a perfectly normal response to G 30 320. If no one else has any contribution about the value of G 30 320 in sulphone resistance, let us proceed to the problem of lepra reaction.

4. REACTION—NEW CASES

CHAIRMAN: One panel on reaction—which was, I think, at the Madrid Congress—talked about lepra-reaction and erythema nodosum leprosum. The panel on reaction at the last Rio Congress spoke about leprosy-exacerbation, which was the old lepra-reaction, and about lepra-reaction, which was the old erythema nodosum! As Dharmendra subsequently wrote: "They made confusion worse confounded". If you are speaking of reactions in lepromatous
leprosy, which produce erythema nodosum leprosum (ENL) skin-lesions, may I suggest it might be helpful if you call them “erythema nodosum leprosum”, no matter what the last panel said. Then we shall at least know that you mean the reaction that occurs in lepromatous leprosy, giving ENL skin-lesions often accompanied by neuritis, iritis, orchitis and arthritis as well. If you are talking about reaction in non-lepromatous patients, please make that quite plain too.

I suggest that we take lepra-reaction in 2 stages: first, in previously untreated patients, especially lepromatous cases—what is the incidence of reaction to ENL, whatever you like to call it, during a standard course of anti-leprosy treatment? Second, what is the effect of treatment with G 30 320 compared with steroids, potassium antimony tartrate, aspirin, chloroquine, etc., on established reaction?

How much ENL do we see in new, previously untreated patients, undergoing their first course of treatment? Dr. Stanley Browne was the first person to comment on the possible anti-inflammatory action of G 30 320 in his original series of patients, and I should like him to start the ball rolling.

DR. S. G. BROWNE: I shall attempt to abide by the Chairman’s definition of “reaction”. I shall sometimes use the word “reaction” and sometimes “ENL”. Leprologists of long experience have seen acute reaction in untreated patients with lepromatous leprosy.

In our early observations (I include my friend and colleague, Dr. Hogerzeil, who was my co-worker), we observed that 2 patients with lepromatous leprosy developed acute reaction during the first 3 weeks of G 30 320 treatment. After that, no patient in the series developed acute reaction. This suggested to us the possibility that G 30 320 might have some action in suppressing the development of acute reaction in lepromatous leprosy. No claims were made at this stage, because this could easily have been a self-limiting, transient phenomenon which, as we all know, occurs not infrequently in lepromatous leprosy.

In subsequent series of patients under G 30 320 treatment for lepromatous leprosy, I have personally observed only one patient who has developed acute reaction during adequate therapy with G 30 320—adequate in the sense of producing clinical and bacteriological amelioration. This occurred after 3 months of treatment and responded to doubling the dose from 100 to 200 mg/day. These early observations naturally required rigorous examination not only in Africa, where acute exacerbation in lepromatous leprosy is both less frequent and less severe than amongst the less deeply pigmented peoples, but also in India, and further East—Korea, the Philippines, Malaysia, etc.

That, Mr. Chairman, is as far as I would go with the role of G 30 320 in preventing lepra reaction developing in patients who, to the extent of one-half to two-thirds, might be considered prone to develop such reaction during the initial course of treatment of leprosy.

DR. W. JOPLING: One can forecast the patient who is likely to develop ENL reaction from the commencement of treatment by a study of his B.I. and M.I. If nearly all a patient’s bacilli are in a solid-staining form, about 6 months will elapse before he develops ENL. The majority of my patients, of course, do develop ENL—the majority of patients or those who develop ENL are light-skinned. On the other hand, if a patient has a preponderance of fragmented and granular bacilli at the time we first see him, treatment may precipitate ENL reaction within a matter of a few weeks. I think this is the important thing to get clear in the first place.

DR. D. LEIKER: We have given G 30 320 to 9 previously untreated patients, who had not shown reactions (ENL) in the 2 years prior to G 30 320 treatment. Eight did not show any reactions during periods of G 30 320 treatment ranging from 11 to 30 months; one patient showed a single reaction. On the other hand, among 16 lepromatous patients with complications prior to G 30 320 treatment, 12 have shown one or more ENL reactions while receiving the drug.

In none of the patients was evidence found that the reactions were provoked by or became worse during G 30 320 therapy. In 9 patients,
Colour Plate. The response to treatment with Lampson (see text).
reactions did not recur after the first few months of treatment. In one patient the reaction stopped after 3 months, but recurred in mild form after 8 months of treatment; 3 months later, it stopped again, and has not recurred. In 2 patients G 30 320 did not seem to make any difference. The reactions became worse and we had to give high doses of steroids. In one of them the dosage of G 30 320 was increased to 300 mg/day and that again did not make the slightest difference—the 2 patients died. Unfortunately, this happened right at the beginning of the trial which worried me very much. Autopsy was performed and we found no evidence that death had anything to do with G 30 320. In one case the cause was quite obvious—a perforating ulcer due to prolonged high dosages of steroids. In the other case the cause of death was not discovered, but G 30 320 was probably not the cause; no evidence in the liver, spleen or other internal organs suggested that it had anything to do with the drug.

CHAIRMAN: The second patient, cause of death unknown, was he in severe ENL reaction at the time of death?

DR. D. LEIKER: He had continuous reactions and each time we had to increase the dosage of steroids. As soon as the reaction subsided, we tried to reduce it gradually again from dangerously high levels. Immediately severe reaction developed, and we had to raise the dosage again, and this happened 10 or 15 times within 7 or 8 months. Gradually the general condition deteriorated and the patient died. There was an abscess from which salmonellae were cultured. This may have had something to do with the death.

CHAIRMAN: You said you increased the dose of G 30 320 in one patient to 300 mg a day. What was your standard dose?

DR. D. LEIKER: 100 mg/day in all cases.

DR. M. H. PEARSON: Our experience with G 30 320 in patients previously either untreated or resistant to other drugs—and in effect untreated—before G 30 320 was given is consolidated in Table 1. The columns labelled “ENL, 1 2 3 4” represent degrees of severity of ENL. Roughly, Grade 4 means a reaction needing large doses of steroids, and Grade 3 small doses, while Grade 2 patients can just be managed without steroids, and those in Grade 1 have a very mild reaction. The top 2 sections show the incidence of ENL in patients treated with 100 mg of G 30 320 3 times a day. I should emphasize that these were all pure lepromatous patients at biopsy; no borderline-lepromatous (BL) cases were included in Table 1. In one of 16 cases treated for 6 months minimal ENL developed in the first week or 2 of treatment and then subsided. Four continued on G 30 320 3 times a day for another 6 months.

During that period one patient developed moderately severe ENL, which was transient but needed steroids for a short period. He had had very severe ENL previously and was sulphone-resistant.

Among the patients given 100 mg of G 30 320 daily, 5 were treated for 6 months, one developing mild ENL of Grade 2. Eight were treated for 6 to 12 months, some having previously received 300 mg daily; others continued on 100 mg daily from the initial treatment. Three of these developed ENL, 2 fairly seriously and one moderate. Of 6 patients who continued treatment for 12 to 18 months, one developed ENL mildly, while no reaction was seen among the 8 patients treated for between 18 and 30 months with 100 mg daily. In a series of 9

<table>
<thead>
<tr>
<th>Dose of G 30 320</th>
<th>Period (months)</th>
<th>No. of cases</th>
<th>No. of developing ENL</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg t.d.s.</td>
<td>0-6</td>
<td>16</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>6-12</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>100 mg daily</td>
<td>0-6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6-12</td>
<td>8</td>
<td>1 1 1</td>
</tr>
<tr>
<td></td>
<td>12-18</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>18-24</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>24-30</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>100 mg 2 or 3 times weekly</td>
<td>0-4½</td>
<td>9</td>
<td>-  -  -  -</td>
</tr>
<tr>
<td>12-18</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18-30</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-36</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 2

Incidence of ENL during treatment with dapsone

<table>
<thead>
<tr>
<th>Group</th>
<th>Early (0–6 months)</th>
<th>Late (6–12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepromatous leprosy (LL) treated with dapsone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg twice weekly</td>
<td>4/16</td>
<td>6/14</td>
</tr>
<tr>
<td>Lepromatous leprosy (LL) treated with dapsone</td>
<td>10/76</td>
<td>23/70</td>
</tr>
<tr>
<td>300 mg twice weekly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

patients treated with 100 mg twice weekly for 4\1/2 months, there was no ENL, while one of 3 patients who continued to 12 months developed a minimal reaction. The final groups, 12 to 36 months, represents a different group of patients previously treated with larger doses of G 30 320. None developed ENL.

For comparison, Table 2 shows the incidence of ENL in patients treated with DDS in 2 other trials (not carried out simultaneously). Among those given 50 mg twice weekly, 4 out of 16 developed moderate ENL in the first 6 months, and a total of 8 (moderate and severe) in the second 6 months. These figures are similar to those from a previous study (lower half of table) using 300 mg of dapsone twice a week. Comparison with the results in G 30 320-treated patients suggests a lower incidence of ENL with G 30 320 than with standard dapsone therapy.

Chairman: Thank you, Dr. Pearson. We have now discussed the incidence of ENL in new patients getting G 30 320 as their first drug and Dr. Pearson’s figures compare it with the incidence experienced with dapsone in the same leprosarium. However, I think it is only fair to point out that this was not under controlled conditions. The patients were not admitted and allocated by random selection to one group or another. Once again, one would like to have an absolutely controlled trial, but I am personally quite impressed with those figures.

5. ESTABLISHED REACTION

Chairman: Next, we should like to discuss the value of G 30 320 in patients with established reaction. This is a subject that has aroused some controversy in the leprosy press.

Dr. Jose Barba Rubio: Knowing that the reaction in some cases can disappear without any treatment and, in others, does not disappear in spite of everything that is done, we made a selection of patients with very severe reactions.

The 10 patients chosen suffered from continuous and prolonged lepra reactions and, with only one exception, they had had to suspend every treatment that was tried. The initial dosage of G 30 320 was 300 mg daily, reduced to 100 mg once the reaction was controlled.

The results were very good in 3 cases, good in 4, fair in 1, and bad in 2. Of the 10 patients, 7 are now under treatment with dapsone in doses of 100 mg daily, and one is having thiambutosine. In one case with neuritis before treatment with G 30 320, the neuritis continued and increased. Generally, I believe that G 30 320 is a good drug in those cases where other drugs fail to control lepra reaction.

Dr. S. G. Browne: The original observations on the curative role of G 30 320 in established acute reaction showed that the drug appeared to be effective in 10 patients with severe Grade 4 or 3 reaction of long duration (16 to 36 months, with an average of 24 months). The duration of treatment in these patients before reaction began had been as follows: 5 patients, 5 to 9 months; 2 patients, 10 to 19 months; 3 patients, over 20 months. They were all severely ill and corticosteroid dependent. On many occasions, other anti-inflammatory drugs had been prescribed, but to no effect. Repeated attempts at weaning from corticosteroid dependence had been made without success. Invariably reaction was precipitated by a slight reduction in steroid dosage. When these patients with established severe reaction started G 30 320 treatment, they were steroid dependent to the tune of 10 to 15 mg prednisolone daily. Even
when controlled on this dose, 10 mg of dapsone was sufficient to precipitate acute exacerbation.

This trial, and other similar trials with which I have been associated, used the patients as their own controls, to determine the lowest maintenance dose of corticosteroid that could be given. G 30 320 was then introduced, beginning with 100 mg/day, and the steroid dosage gradually reduced. If reaction reappeared, then the dose of G 30 320 was increased. It was found that all patients could be weaned from corticosteroid dependence, by giving G 30 320 alone. The maintenance dose of G 30 320, which depended on the circumstances, was 100, 200 or even 300 mg/day, the higher dosage being gradually reduced until, in some cases, reaction reappeared. The quantity was then increased again in order to control the reaction completely. In all patients it was possible permanently to control the reaction and then gradually to increase dapsone as a therapeutic agent.

CHAIRMAN: Dr. Browne emphasizes the importance of some sort of control, and the method of using the patient as his own control is one of the possible ways of doing a controlled trial in erythema nodosum leprosum or lepra reaction—whichever name you prefer. Next, I would like to call on Dr. Hastings, who has recently published a paper on G 30 320 and ENL.

DR. HASTINGS: Briefly, we attempted to match 6 pairs of patients with chronic ENL, requiring corticosteroid therapy. They were divided into 2 groups and we attempted to match, as accurately as possible, age, sex, severity of ENL and so forth. Generally they had pure lepromatous leprosy with erythema nodosum. We measured the steroid requirement to prevent significant neuritis and ulcerating erythema nodosum, and, in the course of some 6 months, we felt that the G 30 320 group, which averaged 216 mg/day, did better than a comparable group treated with solapsone. I might add that each dose of the G 30 320 was swallowed in the presence of nurses on duty, and the solapsone was, of course, injected, so we felt that all patients were indeed taking the drug in full measure.

DR. IMKAMP: I can only confirm the findings of Dr. Browne. Our trial consisted of 18 severely ill, corticosteroid dependent lepromatous patients, who, after an average of 2 years and 7 months of steroid treatment, were started on 100 mg G 30 320 daily, except in one case, who started with 200 mg daily. All were eventually weaned off prednisolone; the dose of G 30 320 was increased according to individual needs, no patient getting more than 400 mg/day. Out of 8 female patients, 7 have been changed to dapsone after an average of 22 months on G 30 320, and 14.4 months after the ENL was controlled. Of the 10 male patients, 7 were changed to dapsone after an average of 22.2 months on G 30 320, and 14.4 months after the ENL was controlled. All those patients improved in health, and were eventually discharged from hospital; several are already discharged from the leprosarium.

One patient with pure lepromatous leprosy, sent to us by another doctor because she could not be treated with any leprosy drugs, had continuous ENL and could be controlled only with 5 mg of prednisolone twice daily. When she arrived she was in fairly good condition, the ENL was controlled, the B.I. 5, and the M.I. 0%. We gradually decreased the prednisolone without giving any anti-leprosy drugs, and ENL developed when she was having 5 mg prednisolone. We gave her first a course of stibophen, but she did not respond, and then we gave her 100 mg G 30 320 daily. About 10 days later she walked, and starting eating. Her temperature was normal and gradually she became stronger; her ENL was completely controlled on 100 mg daily. Then we ran out of 1 mg tablets of prednisolone and made up a suspension, gradually reducing the dosage by 1 mg a month. Then in July, when she was on 2 mg and reduced to 1 mg, she had another bout of ENL. We were then told that the suspension was probably not stable, and she may have been receiving much less than we expected. She developed laryngeal oedema and G 30 320 was
increased to 400 mg but prednisolone remained at 1 mg daily, and she was treated with oxygen. She recovered completely. We now had taken off 0.25 mg of prednisolone; 2 days later she had a slight temperature of 99° (37.2) and a swollen lip which responded to an increase of G 30 320 from 300 to 400 mg. She has done very well, and we intend to decrease her prednisolone by 0.25 mg every month.

DR. W. JOPLING: My experience with G 30 320 has been in the management of lepromatous cases with ENL reactions, and there are 2 groups that I should like to report briefly upon. In the first instance, about 5 years ago I tried with a small group of 5 patients giving very small doses of G 30 320, 25 or 50 mg twice a week. Over several months of observation, I found no improvement whatsoever in ENL reactions. The second group consists of 24 patients all with severe ENL reactions, 8 of whom had to be controlled by steroids. In all these 24, a minimum of 100 mg G 30 320/day and a maximum of 400 mg/day completely controlled the erythema nodosum reactions. The importance of increasing dosage with need was brought home to me with a patient from Liverpool, who was on TB 1 (thiacetazone) treatment because he is sulphone resistant. He developed erythema necroticans—a necrotic, bullous, form of ENL—and I let him return to Liverpool. (Most of my patients are out-patients; they have no ENL in hospital, but when I send them out to work, down they go with ENL, because by that time there is sufficient granularity of their bacilli.) He phoned from Liverpool to say: “I have taken G 30 320 for a month, 100 mg a day, my erythema necroticans is no better; I am in a pitiful condition, covered with sores.” I replied: “Don’t come to London, increase the dose of G 30 320 to 300 mg a day”, and I had a letter 2 or 3 days later saying: “Wonderful, entirely under control”.

CHAIRMAN: Thank you, Dr. Jopling, I am very interested to hear of your further experiences. The speakers so far have all been in favour of G 30 320 in controlling reactions, although Dr. Jopling has pointed out the importance of dose. Dr. Pettit published a carefully designed trial about 2 years ago, which was not favourable.

DR. PETTIT: I am the one that caused all the trouble. If I can introduce myself, I started as a dermatologist, and I am doing mainly dermatology now. I have seen many diseases, as all dermatologists have, which are fluctuant in their course. This makes it very difficult, not only to design clinical trials, but also to make any assumptions on cases that get better 3 days after treatment has been changed.

Maybe people have a little more optimism than I have, and have been anxious to see some patients improve and have not always waited for the full effect of long-term treatment. Dr. Barba-Rubio for instance, in his series of cases had 3 very good successes and 2 almost total failures. You might assume several things from that. Dr. Browne’s cases, which were corticosteroid dependent at a dosage of 10 to 15 mg of prednisolone a day, are not what I would have called very bad cases when I was writing this paper. Dr. Imkamp’s case that could be ameliorated to some extent by 1 mg a day, I would not have called a severe case of erythema nodosum leprosum. [Dr. Imkamp comments: As a measure of precaution, the dose of prednisolone was reduced by this amount.]

In other words, perhaps the cases that I was working on were more severe than the average. It has already been pointed out that in the East, among the Chinese and the paler-skinned patients, reactions are more severe as well as more frequent. So may be our bases of comparison were not comparable from one country to another. In carrying out a trial of any drug, surely one must maintain the dosage. It is no good playing a game of roulette; the way to win at roulette is to double up. But it is not scientific to say: “If you do not get a response with 100 mg give 200, and if 200 does not work, give 400”. As the years go by, you are bound to get a success now and then. It seems to me that if you are going to do a trial you must decide to give such a dose for such a type of disease. The trial I did was an attempt to see whether
100 mg/day works on very severe cases of ENL. Really it was not terribly convincing. If 300 mg/day works in less severe cases I have no experience. I would suggest that the subject is not totally closed.

CHAIRMAN: Dr. Pettit has brought up 2 or 3 points. First, the importance of careful methodology in the design of these trials. Second, the one I mentioned, the importance of dose, and thirdly, the need to take into account the different regions and different races when interpreting results.

DR. E. J. SCHULZ: I hope my trial will be approved by Dr. Pettit. It consists of 2 sections. The first is a comparison of ENL patients before and after the use of G 30 320. There were 28 patients, all having prednisone for varying periods, with an average of 17 months at a dose of 5 to 40 mg daily, even 50 mg in one or 2 cases. At the start of the trial, we gave all patients 100 mg G 30 320 daily. This was increased to 200 mg after 2 weeks, then 300 mg. Later, as we found larger doses to be necessary, some patients were given an initial dose of 200 mg. In 5 cases, it was necessary to increase the dosage to 400 mg daily. The aim of this trial was to control ENL, stop prednisone and continue dapsone (which is given at our institution in a dose of 300 mg a week). The prednisone was stopped in 68% of these patients after 5 months on average, decreased in the others, and all patients improved. Very important was the fact that it took about 5 months for the patients to reach their maximal response; in one or 2 cases the ENL became a little worse shortly after G 30 320 was started. 400 mg daily was necessary in 5 patients, 300 mg in 20, 200 mg in 2, and 100 mg was sufficient in only one patient. None failed to respond.

The second trial contained 2 groups, treatment and control. The first consisted of 16 patients receiving dapsone 300 mg weekly plus G 30 320, 100 mg daily. The second group consisted of 15 patients receiving 300 mg dapsone weekly. All patients had pure lepromatous leprosy and the trial was conducted over a period of 18 months. At the start of treatment, there were 6 ENL patients in each group. After 18 months, there were 11 ENL patients in the group treated with dapsone only; in other words the number of reactions almost doubled. In the group receiving G. 30 320 as well as dapsone, the number of reactors fell by half, from 6 to 3.

CHAIRMAN: Once again the question of dosage crops up. I believe, Dr. Pettit, you used a standard dose of 100 mg daily, 6 days a week.

DR. J. PETTIT: Steadily, regularly, 6 days a week.

CHAIRMAN: This has to be borne in mind in comparing your results with the others we have been listening to.

DR. GRACE WARREN: I have presented some of our findings in the treatment of reaction in a paper, a summary of which is printed on page 60 in the book of abstracts. The trial was designed after the style of Dr. Browne’s, using the patient as his own control.

The 30 patients had all been in hospital with chronic erythema nodosum leprosum for a minimum of 2 years, some of them for 4, 5 and 6 years; and 4 of them were on prednisolone. I will not say they were prednisolone dependent, because only one of them was on a fairly high dosage. We aimed at finding out the dose of G 30 320 required by these patients, and the majority commenced at 300 mg/week. This was increased every 4 to 6 weeks until the reaction was controlled. Three patients required only 300 mg/week, 13 patients required 600 mg, 9 patients required 900 mg, and 4 patients required 1200 mg/week. Once all reaction had been controlled for a minimum of 6 weeks, we attempted to reduce the dose of G 30 320, and this is where we began getting some very interesting findings.

In some patients who initially required 900 mg, we were able to reduce to 400 mg a week, whereas some patients could not tolerate any reduction. They would go back into erythema nodosum leprosum—though not immediately, and I have not seen an increase of G 30 320 control reaction within a few days either. Maybe I have not increased it enough. Increased dosage usually takes a fortnight at
least to make much difference in reaction. Because this is a fluctuating complaint, we did not alter our dosage more often than once every 4 or 6 weeks; so that we had enough time to see whether spontaneous alteration would take place. I mentioned earlier the boy with neuritis who relapsed, and we have had one or two other cases who appeared stable on low dosage and then suddenly went into a reaction again, but in no case were these reactions as severe as they had been before the patient was on G 30 320.

I was interested in the comments we had earlier on the cases which failed to respond. We had one patient (No. 1333) on 20 mg prednisolone for 12 months who, 8 weeks after commencement of G 30 320, went into an extremely severe ulcerating type of reaction. We did not stop the G 30 320 or change the dose of prednisolone. Eventually she came out of reaction and after 6 months she was completely off prednisolone, and is now on 1200 mg of G 30 320 weekly with good fall in the B1. She gets an occasional mild ENL—one or 2 spots at a time—of purely nuisance value. Her general condition is now so much improved that she has requested discharge after over 18 months in hospital.

**DR. K. MAHMUD (Djakarta):** My trial with G 30 320 was started 3 months ago, so this is only a progress report, but nevertheless it confirms the other trials reported. As you know, in Indonesia, we also have trouble, especially with patients developing reactions on sulphone. We first tried G 30 320 in 13 patients, all admitted to the leprosarium, 7 of them previously controlled by corticosteroid or other anti-reaction drugs. We started G 30 320 at 100 mg/day for 6 days, and then increased dosage to 200, 300 mg and so on to control reactions. After 3 months, 4 of the 13 patients had no reaction at all, with improving general condition and falling erythrocyte sedimentation rate. They feel quite happy that they are free from the burden of suffering after many years. The other 9 patients had reactions, controlled in 5 by G 30 320, 200 mg/day, in 2 by 300 mg/day, and in one by 400 mg/day. In the final case we increased the dosage to 600 mg/day, but still could not control the reaction without 15 mg of prednisolone daily. But now we are decreasing the steroid dosage, and I think we shall have the same experience as our colleagues here. Of the patients who developed reactions, 4 only had one and up to now there is no further reaction; 4 developed reactions for a second time after 3 or 4 weeks, but the second was milder and shorter in duration.

One of the patients, who was really sick when admitted to the leprosarium, improved remarkably after only one month. Before starting G 30 320 he could not walk and was bedridden. After 3 months his weight increased by 10%, and he could walk.

**DR. KARAT:** Concerning methodology, I should like to point out that the very faults which Dr. Pettit pointed out in the other trials apply to his own, namely, that there were 2 variables; first the subjective interpretation of severity of reaction to determine steroid treatment. And second, as I interpret his paper, the steroid dose given went up and down, depending on the clinical status of the patient. I do not see how adjustment of the G 30 320 dose differs in principle from adjustment of steroid dosage.

Briefly, 23 cases were under trial in my group, of which 4 were not on a controlled trial; 2 of them needed 30 mg of prednisolone/day, one needed 45 mg/day, and another 60 mg/day, for periods ranging from 18 months to 2 years. All of them came to me with hypertension and Cushingoid facies, still having almost continuous episodes of necrotizing erythema nodosum with haemoglobin ranging from 6 to 8 g. These people were given 300 mg of G 30 320/day, and the patient needing 60 mg of prednisolone took 12 weeks before he became completely controlled, with no further steroids. In all cases, steroids were withdrawn in between 2 and 4 weeks, using intermittent administration of ACTH. On admission, prednisolone was stopped overnight, and patients received on alternate days injections of long-acting ACTH. In all, steroids were completely withdrawn and the erythema nodosum leprosum (which was 4+ if not 5+, in severity in this group) was controlled. Among the 19 control patients, 10
belonged to the prednisolone group, and 9 to the G 30 320 group. In the latter the average duration for control of reaction ranged from 14 to 28 days. No first reactors and no patients below $3+$ in severity were admitted into the series. The average number of reactions in these patients was 30 prior to admission to trial. I would consider them severe reactions by any standards, anywhere in the world.

CHAIRMAN: There is obviously a lot to discuss here, and I would like to ask just one or 2 questions before we stop. What I am particularly interested in with regard to lepra reaction and ENL is whether there is an absolute suppressive dose of G 30 320. I have been noting down the doses that contributors have suggested; some patients were controlled by 200 mg, some by 400 mg/day, and one patient was not controlled even by 600 mg/day. So it looks as if there is a variable range. I wonder if anybody is quite sure that he has found an absolute suppressive dose? How about the permanence of the controlled state once the reactions have been brought under control? Have we seen a picture emerging of any special time limit at which it is safe to take patients off G 30 320 perhaps, and put them back on to dapsone?

DR. F. IMKAMP: Yes. My patients were taken off G 30 320, 14.4 months after their ENL was controlled, and put on a low dosage of dapsone 22 months after the G 30 320 treatment started.

CHAIRMAN: Thank you. This is a point we have to note, and I hope those who are preparing papers will stress it. We have been interested to see how long patients have been kept on G 30 320 before returning to dapsone, and the relapse rate of reactions afterwards or while still on G 30 320.

We are deliberately avoiding all experimental work. Otherwise, I would have asked Dr. Vischer to report on his experimental work on the anti-inflammatory action of G 30 320, but those of you who are staying for the Congress will hear him report it there. However, I was this morning informed that the leprosy research group at the National Institute for Medical Research did find an anti-inflammatory action of G 30 320 in mice, using the carrageenin test, but no immuno-suppressive activity against skin homograft rejection in mice.

6. PIGMENTATION AND TOXIC EFFECTS OF G 30 320

CHAIRMAN: We have not, I am afraid, discussed toxicity and side-effects, or pigmentation. A question I would like to ask—I think Dr. Stanley Browne probably has the answer—is how long does pigmentation persist after stopping G 30 320?

DR. BROWNE: It varies with the initial degree of cutaneous pigmentation, and with the degree of pigmentation produced by G 30 320, which in turn, may or may not depend upon the dose given. I am sorry to be so vague, but all these things are variable. Pigmentation may disappear within 3 months; it can persist up to 18 months, sometimes as diffuse hyperpigmentation, of slatey-grey appearance, either in the lesions themselves, especially when they are thick and fibrotic, or in apparently normal skin.

DR. G. WARREN: Three of my patients have been off G 30 320 for 3 months; so far there is some obvious noticeable change, but they are still definitely pigmented, though this is fading.

DR. L. HOGERZEIL: When I went back to Holland, I saw leprosy patients such as I had very seldom seen in Biafra in the years I was there. I have tried G 30 320 on 6 patients who had previously been treated for an average of 16 years each. This was almost unknown in Biafra; they were all resistant to thiambutosine and all intolerant of dapsone. They were just drifting on, given steroids intermittently in dosages between 30 and 60 mg. They have now been treated with G 30 320 for 1½ to 2 years. It was 9 months to a year before the first reactions reappeared in much milder form, and after
about half a year it was possible to resume very low dosage of sulphone. In the 2 years that we have treated these poor patients in Holland, they have begun to make some progress comparable to that normally seen with dapsone. This was out of the question in the previous 14 to 16 years.

TOXIC EFFECTS

CHAIRMAN: Various authors have described gastro-intestinal upsets on daily doses of 300 mg of G 30 320 and above.

DR. D. LEIKER: We have had 2 patients with mild gastric complaints which did not become more serious on G 30 320. I have had to take one other patient off G 30 320 because he had very serious stomach complaints; he vomited and developed a gastric ulcer. Is this exceptional? We switched him over to DPT and had the same results, again gastric complaints. We switched over to thiosemicarbazone and had the same complaints. This, I would say, is exceptional.

CHAIRMAN: Has anybody reported or seen gastro-intestinal upset in doses under 300 mg a day?

DR. D. LEIKER: This patient was on 100 mg/day.

CHAIRMAN: But this was a patient who was having multiple gastro-intestinal upsets. Dr. Hastings, you had a case?

DR. R. C. HASTINGS: We have seen a number of gastro-intestinal upsets in patients receiving 200 mg daily or less.

DR. GRACE WARREN: Some of our patients were complaining of gastro-intestinal disturbances, but when they took their G 30 320 with their main meal of the day we found that everything settled down. That included a number of patients known to have had gastric ulcers before we started and who had no increase in symptoms, which had been controlled by probanthine before G 30 320 was started.

CHAIRMAN: Has anybody observed any other toxic effects, such as dermatitis or leucopenia or anything?

DR. E. J. SCHULZ: I have seen a few cases of dermatitis, but in none could it be shown that G 30 320 was the cause, because the dermatitis disappeared in spite of continued treatment. The results of examination of a patient who came to post mortem 8 months after he had last taken G 30 320 showed no crystals in the jejunal mucosa. Prof. Simson (who does our pathology) reported that crystals were observed in the cortical tubules in the kidney that were similar, or identical, to those of G 30 320.

PROF. J. GATTI: In 15 patients, we observed after 4 or 5 weeks of treatment that the skin became xerodermic, and in 4 cases frankly ichyosiform. The xerodermia may explain the generalized itchiness that was observed on 2 patients. We did not see alopecia.

DR. W. H. JOPLING: Four out of 24 patients (16%) had a generalized pruritus which improved on reduction of dosage. These patients were having 200 mg or more a day, coming down to 100 mg. In no case was it necessary to cease therapy.

DR. S. G. BROWNE: We had one case of exfoliative dermatitis that may or may not be attributable to G 30 320, but certainly occurred during G 30 320 treatment, 100 mg daily; 2 patients complained of giddiness one hour after taking G 30 320, 100 mg capsule on an empty stomach; there again, I would hesitate to attribute that to G 30 320. On the other hand, I have seen a patient elsewhere who was complaining of a severe gastric upset on 200 mg of G 30 320, but when he saw how greatly improved he was and how his fellow patients were getting better on G 30 320, he had no further trouble.

DR. P. D. FOWLER: We have not had any bone marrow toxicity reported that has been definitely related to the drug. One case has been very recently reported in London of a child taking, I think, 200 mg daily over a period of about 4 or 5 months, whose polymorphonuclear leukocytes went down to rather low levels. The dose was reduced, but treatment was not stopped; in this case the white cells rapidly recovered. It was suggested initially that this might have been a toxic reaction to G 30 320, because it was the only drug the child was taking. But in view of the fact that there was a natural recovery while the drug was still continued, this now seems rather unlikely.
7. EFFECTS OF G 30 320 ON PREGNANCY AND LACTATION

CHAIRMAN: I would like to know if anybody has experience of the drug in pregnancy or lactation.

DR. F. M. J. H. IMKAMP: Three patients, after being over a year on G 30 320, were delivered of female babies, all normal. One child unfortunately died because the mother, in spite of a warning to come to the hospital and report she was in labour, had one of her friends deliver her in the leprosarium, and the child had subdural haemorrhage (confirmed at post-mortem). Physically all the children were healthy, and skin pigmentation was, I should say, normal, though others thought it slightly darker.

DR. E. J. SCHULZ: We had one patient who took 100 mg of G 30 320 throughout pregnancy and had a normal baby. A patient who took 100 mg from about the first or second month had a premature infant following an ante-partum haemorrhage. A post mortem was done on this baby and there was no sign of any teratogenic action. The findings of epidural and other haemorrhages were apparently those usually seen in premature babies who have suffered from anoxia before birth.

DR. S. G. BROWNE: One patient, a nurse with severe lepromatous leprosy, was treated with G 30 320 in Eastern Nigeria. She was delivered successively of 2 children. Both babies were rather more deeply pigmented than they should have been. The other patient, who was lactating when admitted to the very first G 30 320 trial, passed on some of the drug apparently in her milk and the baby became rather more deeply pigmented, after passing through the phase of ruddiness.

DR. H. S. PETTIT: A patient I was treating for Mycobacterium ulcerans infection with 300 mg of G 30 320 daily, was breast-feeding her baby when the diagnosis was made. Her major complaint was that the milk was a bright pink colour, and the baby certainly turned red. I think we must be aware of this, because if there is going to be renal involvement in adults who take an average dose, there might be danger to the kidneys of a breast-fed baby.

CHAIRMAN: The only relevant patient whom I have personally treated was 6 months pregnant when she started treatment. She was thiambutosine resistant, and had sulphone allergy. I left before I knew the result of the delivery, but she probably had a normal baby, because her treatment was started at 6 months, so there was really no question of teratogenic effect.

So, ladies and gentlemen, I would like to thank you all for your co-operation today. In closing I would like to thank one of the few people whom I have not been able to persuade to speak today, and ask him to say goodnight to us: the discoverer of G 30 320, Dr. Barry. Would you close the symposium, Dr. Barry?

DR. V. C. BARRY (DUBLIN): I am afraid I am hardly qualified to close the symposium, in fact I could not have contributed to it. I enjoyed it very much and I learnt a lot. Strangely enough, I do not know anything about leprosy, but I have read a certain amount about it. I have not discovered, nevertheless, what the difference is between ENL and lepra reaction, but I must say I have enjoyed the proceedings very much. My colleagues and I have been working for 21 years on these compounds. The first lead we got was in 1947, and we have now tried 300 similar compounds. None of them is more active than G 30 320 so far. But we have not given up.
In the light of the preceding discussions, it would seem appropriate to summarize current knowledge of G 30 320 as a guide to the practical use of this relatively little-known drug in the treatment of leprosy.

**TOLERANCE AND CONTRA-INDICATIONS**

From answers given to a questionnaire distributed at the symposium, the reports were based on a total of 718 patients. Of these, 533 had lepromatous leprosy, 9 tuberculoid, one indeterminate, and 87 borderline, while 88 had had leprosy of unspecified type. The drug has therefore been used in a considerable number of patients in many countries, and no serious toxic effects have been reported with the possible exception of one case of exfoliative dermatitis. Mild gastro-intestinal upsets, occurring in a few patients, have responded to lowering of the dosage. Drug sensitivity rashes have been rare and have been easily controlled. The report of temporary, microscopic abnormalities in the urine requires confirmation and study at other centres. No serious blood dyscrasias have been reported to date.

In general, no definite contra-indication has as yet been discovered for G 30 320. The drug can probably be used safely for out-patients as well as in-patients, provided that the former are examined regularly both at the beginning and at intervals during the course of treatment. Nevertheless, it is recommended that whenever possible regular blood counts should be carried out together with careful checks of the hepatic and renal functions. The drug should be used with great care in patients with known hepatic or renal impairment. On general grounds, caution is advisable in pregnant women, especially during the period of organogenesis. In the 4 expectant mothers mentioned in the discussion who received G 30 320 during the whole course of their pregnancy, no sign of any teratogenic effect of the drug was observed. Similarly in experimental rats and rabbits, G 30 320 given in a dose of 5 mg/kg body-weight, caused no damage to the embryo; however, the absence of evidence of damage in these animals does not necessarily preclude a teratogenic effect in man. Therefore, in treating pregnant women with G 30 320, the unknown risk to the embryo must be balanced against the indications for giving G 30 320, especially the serious nature of the acute reactions of leprosy that occur during pregnancy. Thus, in erythema nodosum leprosum, the value of giving this anti-inflammatory, anti-bacterial drug must be weighed against the increased risk of abortion or of still-birth in uncontrolled, or steroid-controlled reaction, together with the near-certainty of severe exacerbation of the reaction at the end of the first week of the puerperium. Further experience with G 30 320 in pregnancy is necessary before its use can be fully evaluated or generally recommended for women in the child-bearing period.

The principal disadvantage of G 30 320 remains the drug-induced pigmentation which occurs in most patients. This pigmentation is less acceptable in some races and parts of the world than in others, and patient acceptability must be weighed against the indications for administering the drug. Further research is required on the nature and mechanism of this pigmentation and its reversibility.

**GENERAL ASSESSMENT OF G 30 320**

Although its mode of action against *Mycobacterium leprae* is not yet known, G 30 320 has a definite anti-leprotic effect as measured both in clinical patients and experimentally in the mouse foot-pad infection. Its anti-leprosy activity is of the same order as DDS, although precise evaluation has not yet been carried out, as the results of controlled clinical trials are still awaited. Patients have been treated continuously with the drug for up to 4 3/4 years, and no evidence of drug resistance has been reported. It has been used successfully in the treatment of patients with proven sulphone-resistant leprosy.

There is some evidence that in previously
untreated lepromatous patients receiving G 30 320 as their first anti-leprosy drug, the incidence of erythema nodosum leprosum is less than in similar patients treated with DDS; controlled clinical trials are indicated. In established reaction, the great majority of authors consider that the drug has a very definite anti-inflammatory and reaction-suppressive activity. This is supported by the finding of anti-inflammatory activity in experimental animals as measured by the cotton pellet and the carrageenin tests. However, it has no immuno-suppressive activity, as measured by the classical homograft-rejection test.

**INDICATIONS**

In patients with lepromatous leprosy infected with sulphone-resistant strains of *Mycobacterium leprae*, G 30 320 may be considered the drug of choice; it is fully effective in such patients; proven drug-resistance to G 30 320 has not yet been reported; and, since it is given orally, it is easy to administer. It is the drug of choice in patients suffering from thiambutosine-resistant leprosy who also have allergy to the sulphones. It is indicated in those patients suffering from multiple drug allergies (e.g. from both DDS and thiambutosine allergy), and together with the established second-line anti-leprosy drugs, in those patients who develop DDS allergy. Similarly, it may be considered for any previously-untreated leprosy patient, in whom for any reason dapsone is contra-indicated.

Because of its anti-inflammatory action as well as its anti-leprosy action, treatment with G 30 320 may be considered in the various types of reactions in leprosy and in acute nerve-swelling and nerve pain. In erythema nodosum leprosum, unless the reaction is so mild that it can be easily controlled with the standard anti-reaction drugs (antimony compounds, antimalarials, and mild anti-inflammatory drugs) treatment with G 30 320 should be seriously considered; the other alternatives are dapsone plus steroids, or dapsone plus thalidomide. In non-lepromatous lepra reactions, and in previously untreated non-lepromatous leprosy where it is feared that nerve damage may develop on dapsone therapy, treatment with G 30 320 should be considered as an alternative to dapsone plus steroids.

**DOSAGE**

G 30 320 is given orally, and is available in capsules of 100 mg. The dosage should be adapted to circumstances. In untreated patients with lepromatous leprosy, who receive G 30 320 as their first anti-leprotic drug, 100 mg 3 times a week seems adequate, provided that no ENL has as yet appeared. On the other hand, in sulphone-resistant patients with active leprosy, the minimum recommended dose is 100 mg 6 times a week. These figures apply to patients weighing 40 to 60 kg.

In ENL or in reactions in non-lepromatous leprosy, the individual dose required just to suppress the reaction should be determined. A possible procedure would be to give the patient 200 mg/day for 3 weeks; if at the end of that time the reaction is not controlled, then the daily dose should be increased by 100 mg; if, on the other hand, it is controlled, then the daily dose should be slowly decreased. An increase in the daily dose should not exceed 100 mg in any one week, and as soon as inflammatory signs are under control the dosage should not be increased further. In general, it is suggested that the dosage should not exceed 400 mg/day. There may be a very few patients whose reactions are not controlled even on this dose, and such patients require admission to hospital and careful clinical observation. In such circumstances, under direct medical supervision, the dose could be increased to 500 or even 600 mg/day for a short period or, alternatively, a second anti-inflammatory agent could be introduced. Combined treatment will probably prove to be necessary only in exceptional cases.

Once the reaction has been brought under control, treatment with G 30 320 should be continued for a considerable period; in ENL this will probably be for at least 6 months. Decrease in dosage should be slow in every case,
e.g. by 50 mg/day, and waiting 3 weeks before a further reduction is made. Thus, a patient controlled on 200 mg/day could have his dose reduced to 200 and 100 mg on alternate days; if after 3 weeks no relapse of the reaction has occurred, then the dose may be further decreased to 100 mg daily.

Chronic reactors, or patients who are already in reaction when it is decided to give them G 30 320, are often already receiving steroid treatment. In such patients, the steroid treatment should be continued until the reaction is fully controlled on the appropriate dose of G 30 320. Although it is difficult to give general recommendations, once a patient has been free of reactions for about one month, an attempt may then be made to reduce slowly the dose of steroid. Any relapse of the reaction may then be countered, not by an increase of the steroid dosage but by temporary increase in the dosage of G 30 320, although the needs of each patient must be considered individually. Once the patient requires no further steroids and is stabilized on G 30 320, then the objective is to reduce slowly the dose of the latter drug until the base line dosage for reaction patients of 100 mg of G 30 320 6 times a week has been achieved.

M. F. R. Waters.

CHEMICAL FORMULA AND STRUCTURE
Lampren (G 30 320; B 663) is 3-(p-chloroanilino)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino)-phenazine, formula C_{27}H_{26}Cl_{2}N_{4}, with the following structure: