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PROGRESS WITH NEW ANTILEPROSY DRUGS¹

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The continuing discovery of new drugs possessing chemotherapeutic activity against M. *leprae* is giving the problem of controls in drug trials an ever-increasing importance. Until this work can be relegated to the laboratory, there will be no alternative to the use of human subjects as controls. Some system of selection is needed which not only establishes the activity or otherwise of a drug under trial, but makes possible the direct comparison of one drug with another.

There is no place in drug trials in leprosy for the unfortunate control patient who is simply given a placebo. Any new drug must be judged against the standard set by DDS, and will be of interest only if it has some advantage over DDS, either through increased activity or in freedom from toxic action. It was formerly our practice to choose as controls in drug trials patients corresponding in type and intensity of their infection to those volunteering to participate in a trial, and give them standard DDS treatment (¹). Although this method of individual controls served very well to compare the activity of a new drug with that of DDS, it does not permit the satisfactory comparison of one new drug with another where chemotherapeutic activity is concerned.

A more satisfactory method, and one that appears to meet all circumstances, consists in bringing together the records of as large a number of patients as possible who have had continuous DDS treatment, and producing graphs showing the average decline in bacterial index during DDS therapy at the center concerned. Provided the numbers contributing to it are adequate, such a procedure provides a simple but reliable standard against which it is possible to check the progress of any individual patient, or any group, and thus it becomes possible to compare progress under one new drug with that under another. Over several years a standard of this nature has gradually been built up at Uzuakoli. This is illus-

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trated in Fig. 1,² which covers the progress of the bacterial index during the first four years of treatment in 150 patients on continuous standard DDS therapy, with separate graphs for each degree of positivity up to a maximum bacterial index of 4.0. This standard will improve year by year as more and more patients can be included in it. It is to be expected that similar standards at other centers would show variation in detail.

Before illustrating the activity of certain new drugs against this standard, it is worth while pointing out that when recording a bacteriologic finding it is sound practice to record the condition of the bacilli at the same time. Whatever we may think about the viability of degenerate forms of the lepra bacillus, the fact remains that successful chemotherapy is accompanied by an increasing proportion of degenerate bacilli in routine smears. By estimating this proportion it is possible to observe progress in periods too short for any real decline in bacterial index to be demonstrated. The reappearance of normal bacilli at sites where previously only degenerate forms could be found also gives warning of the exacerbation of the disease resulting maybe from drug resistance. Figure 2 shows the standard form we adopt for this purpose. It covers two occasions of smearing, each at 10 sites, indicates where these are, and makes possible an estimate of the state of the bacilli at every site. Figure 3 shows the form in use in a case showing successful chemotherapy. Figure 4 shows a later stage in the same patient, with a continuous shift to the right in the types of bacilli seen. Figure 5 shows the appearance of an exacerbation of the disease.

Having diverged from the primary object of this paper, let us now compare the progress observed during chemotherapy with three new drugs that was achieved with our DDS standard.

1. THIOUREA COMPOUND CIBA 1906 (DPT)

This substance has been studied extensively in Nigeria, and records now cover nearly 200 patients treated with it alone or in combination for periods up to three and one-half years. Progress reports were made after 16 months $(^2)$ and 32 months $(^4)$. We have found it a very valuable drug, almost entirely free from toxic action in the dosage employed (20-40 mgm./kgm. daily) and possessing chemotherapeutic action at least as good as that of DDS. This is illustrated by Figure 6, which shows the fall in bacterial index displayed by the original trial group of 20 patients up to the 33rd month. In those who have had treatment beyond that time, progress has continued at the same rate up to the 42nd month, with no falling off except with two patients (one of whom is showing an increase in bacilli in his earlobes which appeared at the 40th month).

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²The graphs referred to, not included with the manuscript made available will be published in the full paper in the transactions of the Congress.

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This drug has been found particularly useful for patients who have developed intolerance to DDS, particularly those suffering from neuritis or psychosis. It combines well with DDS and INH, though it is doubtful whether the combination confers any additive effect. Toxic effects have been limited to a mild hypothyroidism encountered in two patients on high dosage during the second year. Garrod (personal communication) has noted infrequency of pregnancy among women taking the drug, probably also the result of a mild antithyroid action. (This may indeed be an advantage rather than the opposite.) The only disadvantage of the drug are its high dosage and high price, which puts it outside the range of mass treatment.

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2. DIAMINODIPHENYL SULPHOXIDE (DDSO)

The second drug inviting comment is DDSO. This drug has now been followed by us in 69 patients for periods up to 33 months, on a standard dosage of 100 mgm. daily, or 400 mgm. twice weekly. A progress report was made after 16 months (³). Chemotherapeutically, its action is at least as great as that of DDS, as is evident from Figure 7, which shows the progress of the original trial group of 17 patients up to the 27th month. It is of interest that the loss of an oxygen atom in the DDS molecule has not robbed it of its chemotherapeutic activity. In some individuals progress has indeed been exceptionally good, and there has been a consistent freedom from neuritis among the patients on the drug. It is, however, a potentially toxic substance. Dermatitis and psychosis have been encountered, and hepatitis has required withdrawal of the drug in two child patients. It may be considered at least as toxic as DDS.

This drug is effective when given twice weekly, and no difficulties have been encountered during the first year of treatment among patients receiving it by this method. Without exception all have made very good progress.

3. DIETHYLDITHIOLISOPHTHALATE (ETIP)³

The third drug to which it is desired to refer is diethyldithiolisophthalate. This oily substance, a derivative of ethyl mercaptan, was shown by Davies and Driver (5) to possess powerful antituberculosis activity in mice, a single dose being effective. Recently (6) the same authors have demonstrated that ethyl mercaptan, which also possesses chemotherapeutic activity, actually exerts its action intracellularly in monocytes. ETIP is thus a drug of considerable potential interest to the leprologist, and it has been under trial in leprosy patients at Uzuakoli for approximately one year. As a detailed report on it will shortly appear, it will suffice here to refer to it briefly.

The drug is not suitable for administration either by mouth or by in-

³Also known as I.C.I. Compound 15,688.

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jection, but as it is readily absorbed through the skin the novel but psychologically sound method of inunction is used. A dose of 3-6 cc. inuncted twice weekly has been found in some patients to exert a powerful chemotherapeutic effect on the bacilli, not only at the site of inunction but generally throughout the body. Signs of degeneration are evident in bacilli within three weeks of the beginning of treatment, and a decline in bacterial index of as much as 1.3 is seen within three months in some individuals. Figure 8 illustrates such a case. No toxic effects have been detected as yet.

Unfortunately, the drug has a disagreeable odor, which needs very careful masking if it is to be acceptable to patients. From this angle it is perhaps a good thing that the administration of the drug need be envisaged only in terms of a short course of a few weeks duration. The fact is that its chemotherapeutic activity, although powerful, is shortlived, and if treatment with it is persisted in for more than three months, drug resistance soon begins to evidence itself. Nevertheless, patients who tolerated the drug for as short a period as six weeks, and then continued treatment with DDS or one of the other drugs already mentioned, have without exception made excellent progress. There seems no doubt that this was accelerated by their preliminary treatment with ETIP.

DISCUSSION

These facts have a wide significance. The possession of drugs with high potency and low toxicity opens up new possibilities in the chemotherapy of leprosy. It was formerly felt that in a lepromatous case the rapid destruction of bacilli might throw a dangerous strain on the patient. In the case of DPT and ETIP this fear, so far, has proved to be without foundation. Patients in whom there has been a rapid fall in bacterial index have not exhibited violent reactions.

It appears not unreasonable to conclude, in the light of these findings, that a sound approach to chemotherapy is to use new drugs like ETIP and DPT during their period of maximum effectiveness, and then to rely on DDS for a sustained effect. In the average case it would be appropriate to initiate treatment with Compound 15,688, continuing this for a few weeks only, and then continuing with DDS. In the same way, DPT effects its most striking action on bacterial index during the first nine months of treatment, and—apart from its use in complications of the disease—this fact, combined with its lack of toxicity, commends its use also early in treatment.

Thus by a succession of drugs, using each to best advantage, there does appear a reasonable hope that the period of treatment could be materially shortened. Experience so far in the few individuals in whom this technique is being followed is very promising.

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SUMMARY

The choice of controls in clinical trials of new antileprosy drugs involves problems which may be best solved, not by using individual controls, but by employing as a standard for comparison the average improvement in bacterial index made by large numbers of patients during standard DDS treatment. Such a standard makes it possible to compare one new drug directly with another. The procedure is illustrated in the case of three new antileprosy drugs, (a) Ciba 1906, (b) diaminodiphenyl sulphoxide (DDSO), and (c) I.C.I. Compound 15,688, or diethyldithiolisophthalate (ETIP).

Ciba 1906, which has now been studied for 3-1/2 years, is an active and valuable drug which nevertheless makes its greatest achievements during the first six months of treatment, when it is usually decidedly superior to DDS. Thereafter its activity approximates that of DDS. DDSO is slower but very steady in action, and has advantages and disadvantages compared with DDS. Compound 15,688 has a remarkable effect in some patients, producing a phenomenal change in the bacterial index and in the morphology of bacilli for a very short time, after which drug resistance develops.

By the judicious use of these drugs during their period of optimal activity, associated where appropriate with DDS, it may be possible to attain new levels of effectiveness in the chemotherapy of leprosy.

RESUMEN

La selección de testigos en las pruebas clínicas de nuevos medicamentos antileprosos plantea problemas que es mejor resolver, no usando distintos testigos, sino empleando como pauta de comparación la mejoría media del índice bacteriano mostrada por grandes números de enfermos durante el tratamiento aceptado con DDS (diaminodifenilsulfona). Una pauta de ese género permite comparar una droga nueva directamente con otra. Queda ilustrado el procedimiento en lo tocante a tres nuevos medicamentos antileprosos: (a) Ciba 1906, (b) diaminofenilsulfóxido (DDSO) y (c) I.C.I. Compuesto 15,688 o dietilditiolisoftalato (ETIP).

El Ciba 1906, ya estudiado 3-1/2 años, es una droga activa y valiosa que, sin embargo, obtiene sus mayores éxitos durante los primeros seis meses de tratamiento, período ese durante el cual suele ser decididamente superior a la DDS. A partir de ahí, su actividad se aproxima a la de la DDS. El DDSO es también más lento, pero muy constante en su efecto, y comparado con la DDS, posee sus ventajas y desventajas. El Compuesto 15,688 ejerce un notable efecto en algunos enfermos, produciendo una alteración fenomenal del índice bacteriano y de la morfología de los bacilos por muy poco tiempo, después de lo cual aparece farmacorresistencia.

Con el uso juicioso de estas drogas durante su período de actividad máxima, unidas cuando parece esto apropiado con la DDS, puede ser posible alcanzar nuevas cimas de eficacia en la quimioterapia de la lepra.

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REFERENCES

- 1. DAVEY, T. F. Testing of new drugs. Leprosy Rev. 27 (1956) 70-73 (correspondence).
- DAVEY, T. F. and CURRIE, G. Clinical trial of diphenyl thiourea compound SU 1906 (Ciba 15095E) in the treatment of leprosy. Progress during the first year. Leprosy Rev. 27 (1956) 94-111.
- 3. DAVEY, T. F., KISSAUN, A. and MONETA, G. The treatment of leprosy with diamino-diphenyl sulphoxide; a progress report. Leprosy Rev. 28 (1957) 51-59.
- DAVEY, T. F. (GARRETT, A. S., NICHOLSON, G., CORCOS, M., FERN, E., MATHE-SON, R. and MACDONALD, A.) The treatment of leprosy with diphenyl thiourea compound SU 1906 (DPT). A report on expanded trials in Nigeria. Leprosy Rev. 29 (1958) 25-44.
- DAVIES, G. E. and DRIVER, G. The antituberculous activity of ethyl thiolesters with particular reference to diethyl dithiolisophthalate. British J. Pharm. & Chemother. 12 (1957) 434-437.
- 6. DAVIES, C. E. and DRIVER, G. W. Personal communication, 1958.

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