BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 1 1960

DEMETHYLCHLORTETRACYCLINE

BY

MAXWELL FINLAND, M.D.*

Associate Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory; Physician-in-Chief, Fourth Medical Service, Boston City Hospital, Boston, Massachusetts, U.S.A.

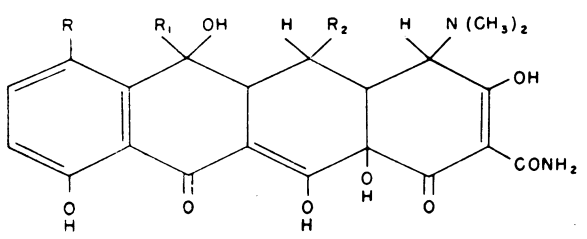
AND

L. P. GARROD, M.D., F.R.C.P.

Bacteriologist, St. Bartholomew's Hospital; Professor of Bacteriology, University of London

A newly discovered antibiotic may either be entirely new or prove to be related in structure and action to another already known. However close a relationship, the discovery may have been worth while if the new member of what may already be a group possesses advantages over the rest in antibacterial activity, pharmacological behaviour, or other properties.

Such a group is that of the tetracyclines, the prototype of which was "aureomycin,"[1] introduced in 1948, followed by "terramycin"[2] two years later. Determination of their chemical structure (Fig. 1) showed that



	R	R_1 =	R_2 =
TETRACYCLINE	H	CH_3	H
CHLORTETRACYCLINE	Cl	CH_3	H
OXYTETRACYCLINE	H	CH_3	OH
DEMETHYLCHLORTETRACYCLINE	Cl	H	H

FIG. 1.—Chemical structure of four tetracycline antibiotics.

these antibiotics differed only in possessing respectively an added chlorine atom and an OH group. A third member of the group, tetracycline,[3 11] was then obtained, possessing neither of these attachments. There were thus aureomycin (chlortetracycline), terramycin (oxytetracycline), and tetracycline[4] ("achromycin," "tetracyn"), which are here referred to as CTC, OTC, and TC.

Differences Between the Older Tetracyclines

It is not to be expected that such closely related substances should differ greatly in any property. Their antibacterial "spectrums" are closely similar, though CTC is usually more active against staphylococci and pneumococci, OTC against *Pseudomonas pyocyanea*, and TC against *Proteus*.[13 17] Cross-resistance between them is complete, whether in organisms resistant when isolated[14] or in those artificially habituated.[15] The discovery of TC was welcomed on other grounds than these. TC produced higher and better-sustained levels of antibiotic activity in the blood than OTC[16] and more particularly than CTC, the exceptional instability of which explains this difference. Moreover, TC was found less apt to produce gastro-intestinal side-effects, notably the acute enterocolitis caused by resistant staphylococci, which had proved to be so dangerous a complication of therapy with CTC and particularly OTC.[5-8]

In a study at the Boston City Hospital,[9] OTC was observed to produce diarrhoea of greater severity and about twice as frequently as CTC. *Staphylococcus aureus* was the only or the predominant organism in the faeces of 27 of the 38 patients with diarrhoea accompanying OTC treatment, but in only 4 of 22 receiving CTC. It had been shown previously that staphylococci were more often resistant to OTC and to a higher degree than to CTC.[10] In a continuation of this study,[12] diarrhoea was found to be much less frequently produced by TC. On the other hand, in a series of 288 cases of pneumonia treated with tetracyclines at St. Bartholomew's Hospital[17] and studied retrospectively by simple summation and averaging of charted bowel actions, it did not appear that there was any significant difference between the amounts of diarrhoea (which was rarely severe) produced by the three drugs. Mainly because of its reputation for being better tolerated the clinical use of TC has largely replaced that of CTC and OTC in recent years.

Properties of Demethylchlortetracycline

In 1957 McCormick *et al.*[18] described a new family of tetracyclines characterized by the absence of a CH_3 group which is found in all others. One of these, demethylchlortetracycline (DMCT) was produced by a mutant of Duggar's original strain of *Streptomyces aureofaciens*, from which CTC had first been obtained. The structure of DMCT is shown in Fig. 1. Its first exceptional property to be demonstrated was a very high degree of resistance to degradation by acid or alkali, and, as will be seen, this stability is a valuable advantage. Its antibacterial activity compared favourably with that

*Aided, in part, by a grant (to M. F.) from the National Institutes of Health, U.S. Public Health Service.

of other tetracyclines. Thirdly, it was found first in dogs, and later in a series of studies in man,[19 20 21] to remain in effective concentration in the blood longer than any other tetracycline. These properties naturally excited much interest, and many further studies of DMCT have been undertaken, the results of 15 of which were presented at the Symposium on Antibiotics in Washington, November 4–6, 1959: 16 further papers on the subject were only "read by title" on this occasion. The text of most of these papers and the findings of other work yet to be published have been made available to us, and the following is a digest of this new information* together with observations of our own.

Antibacterial Action of DMCT in vitro

Reports by 13 different groups of workers, 10 of which have been published,[17 22–30] deal with the susceptibility to DMCT of 3,227 strains of important pathogenic species. A dilution method with twofold differences was used in most of these studies, and comparison was made with TC; often also with OTC and CTC. The almost universal finding was that DMCT was more active than TC by a factor of 2, or of equal activity, but rarely of less. This applies both to Gram-positive organisms and to Gram-negative, the latter including many derived from infections of the urinary tract,[25 26] and to species of *Salmonella* and *Shigella*.[23 29] The more accurate turbidimetric method used by Dornbush and Pelcak[27] showed the factor by which the activity of DMCT exceeded that of TC to vary from 1.1 to 4.8 for different strains of various species, the average being 2.3 for *Streptococcus pyogenes* and about 2.0 for most other organisms. This is the general trend of the findings, but some exceptions were found in a study of 861 strains by Hirsch and Finland,[22] including a lesser relative activity of DMCT against resistant strains of staphylococci.

Against normally sensitive staphylococci CTC is recognized to be more active than TC, and comparison of DMCT with CTC against this organism shows equivalent activity. Garrod and Waterworth[17] compared their bactericidal action and found almost identical initial rates of kill, but as CTC underwent degradation the curve flattened and growth followed, whereas the action of DMCT proceeded to extinction. DMCT may therefore be regarded as CTC with the added virtue of stability.

Absorption, Distribution, and Excretion

Originally demonstrated in dogs by Kanegis and Dearborn, and since confirmed in rabbits by Knothe,[28] the higher sustained levels attained by DMCT in the blood have been shown also to occur in man by three principal studies —those of Sweeney *et al.*,[19] Kunin and Finland,[20] and Hirsch and Finland.[21] The method used was to administer single, or in some experiments repeated, oral doses of DMCT and other tetracyclines to normal subjects in cross-over studies, and to assay the antibiotic in the blood at intervals after a dose, either by the *Bacillus cereus* cup-plate method or by a tube-dilution method using this organism or a staphylococcus, or a haemolytic streptococcus. Results have been expressed in two ways: (1) as w/v—that is, μg./ml. concentrations of the antibiotic in the blood, and (2) as tetracycline equivalents—that is, in terms of the degree of antibacterial activity against the test organisms —thus taking into account not only the concentration attained but the intrinsic activity of each form of tetracycline.

The findings in a series of such tests[20 21] are expressed in these two ways in Figs. 2 and 3. In terms of w/v concentrations (Fig. 2) TC attains the highest levels in the first few hours. DMCT reaches its peak concentration more slowly, and its level declines more gradually,

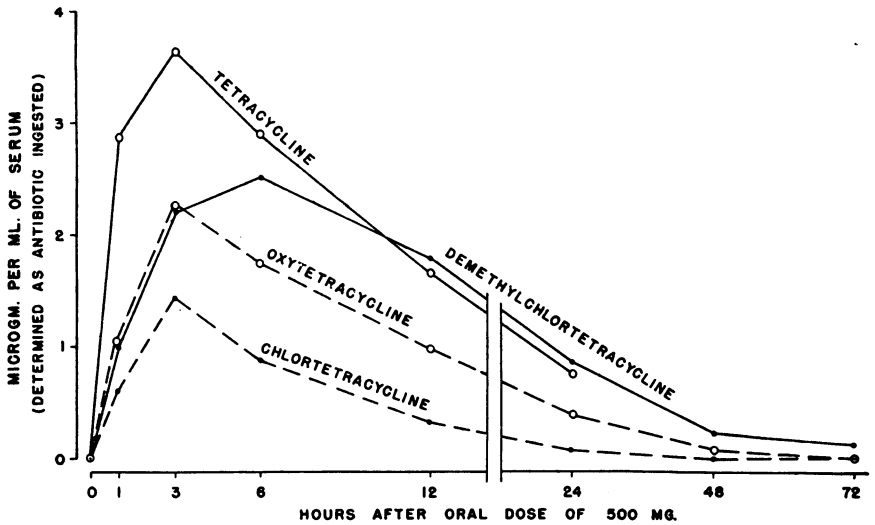


FIG. 2.—Mean concentrations of four tetracycline antibiotics in serum of normal subjects after single oral doses of 500 mg. equivalents of their hydrochlorides (after Kunin and Finland[20] and Hirsch and Finland[21]). Concentrations expressed as weight of administered antibiotic.

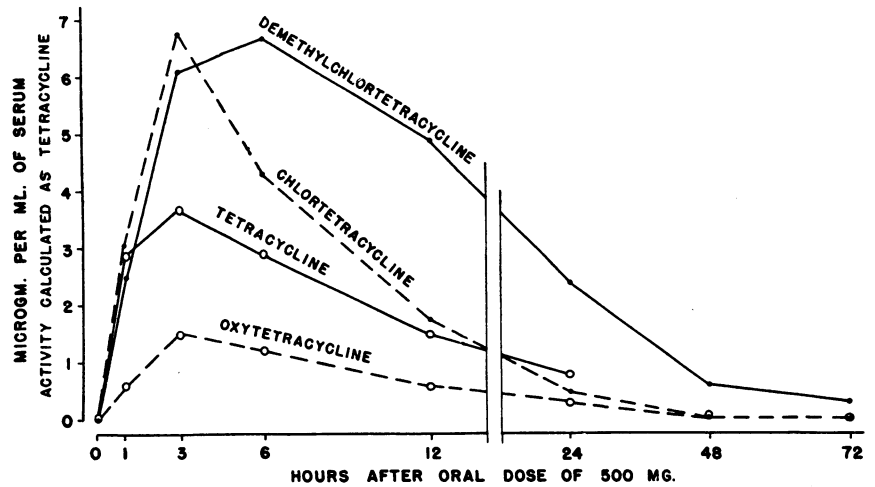


FIG. 3.—Same as Fig. 2. Concentrations calculated as tetracycline activity.

*Only those papers are actually cited here which either have been published or are known to be in press.

so that after about the tenth hour it exceeds that of TC as well as of OTC and CTC, which are lower throughout. This decline is so slow that DMCT is still detectable in the serum after 48 and even 72 hours. When the same results are expressed in terms of tetracycline activity* (Fig. 3) the superiority of DMCT is even more evident, its activity in the blood greatly exceeding that of all three other tetracyclines from the third hour onwards. It was shown[20] at an early stage that the rate of renal clearance of DMCT is only 43% of that of TC, a fact which evidently accounts for its long persistence in therapeutic concentrations in the blood. In these experiments the capsules of tetracyclines other than DMCT contained citric acid or glucosamine hydrochloride to promote better absorption: DMCT itself is not affected by such additions. Further studies[29 31 34] on similar lines, either in normal subjects or in patients undergoing treatment, have yielded generally comparable results, although Perry *et al.*[24] observed consistently lower levels of antistreptococcal activity in serum from 0.3 g. of DMCT than from 0.5 g. of TC; these various findings include confirmation that DMCT (in a liquid formulation) produces good blood levels in children,[36] and observations on urinary excretion: as is to be expected, DMCT appears in the urine later than TC and in lower concentrations.[37]

Detailed studies of distribution and excretion after single intravenous 500-mg. doses (of DMCT also 250 mg.) have been made by Kunin, Dornbush, and Finland.[33] The curves of blood concentrations after administration by this route are shown in Fig. 4. Among the contrasting properties of the four tetracyclines revealed in this study (for data see Table) are the slow renal excretion and consequently much longer "half-life" of DMCT, the rapid removal of CTC by non-renal mechanisms—that is, degradation — and the rapid renal clearance of OTC, of which the greatest percentage of the dose is excreted in the urine. All four were distributed through a relative volume greater than that of the body weight, indicating sequestration in some tissues. In another study Kunin and Finland[34] showed that the concentration of DMCT in bile may be 20–32 times higher than in the serum 7–24 hours after an intravenous dose: like other tetracyclines, it is thus sequestered in the liver. In separate dialysis equilibrium studies,[33] the percentages bound to plasma were found to be TC 24, OTC 20, CTC 47, and DMCT 41.

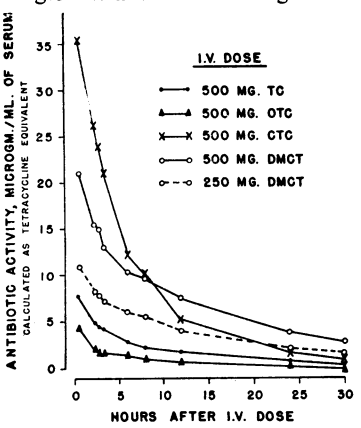


FIG. 4.—Average concentrations of antibiotic in serum of same four normal subjects after intravenous injection of each of the tetracycline antibiotics. Concentrations calculated as tetracycline equivalents. (From Kunin, Dornbush, and Finland.[33])

Penetration into other body fluids.—Boger and Gavin[35] gave single doses of 0.5 or 1 g. of DMCT to 32 patients with uninflamed meninges, and found low levels (1/20 to 1/50 of those in the serum) in cerebrospinal fluid obtained 4–12 hours later. In two other similar studies,[30 37] on only five and two patients respectively, no activity was detected in any specimen of cerebrospinal fluid. One of these papers[30] also records that concentrations equal to those in the serum were found in synovial fluid from two patients undergoing treatment with DMCT.

Distribution and Elimination of Four Tetracycline Homologues After Intravenous Injection in Four Normal Young Men (From Kunin, Dornbush, and Finland[33])*

Rates	TC	OTC	CTC	DMCT	$DMCT_{250}$
Decay in serum (%/hr.)	8·2	7·6	12·4	5·5	6·0
Half-life in serum (hours)	8·5	9·2	5·6	12·7	11·8
Relative volume distribution (% of body weight)	159	189	148	179	148
Clearance from serum (ml. min.)	149	162	205	112	99
Renal clearance† (ml./min. 1·73 M^2)	74	99	32	35	35
Ratio: Clearance of antibiotic% / Clearance of creatinine	62	85	30	27	32
% of dose excreted in 96 hours	60	70	18	39	43
Removal by renal mechanisms (%/hr.)	4·9	4·4	2·9	2·1	2·6
Time required to remove 50% of dose by renal mechanisms (hours)	14·1	16·0	25·9	35·5	27·2
Removal by non-renal mechanisms (%/hr.)	3·3	3·2	9·5	3·4	4·0
Time required to remove 50% of dose by non-renal mechanisms (hours)	21·7	24·0	7·3	20·1	19·1

* Average values after single doses of 500 mg. of each and also 250 mg. of DMCT (designated $DMCT_{250}$); average weight of subjects was 67·8 kg.
† There was no relation to rate of urine flow between 2 and 14 ml./min.

Excretion in faeces.—In a cross-over study in 48 subjects reported by Garrod and Waterworth,[17] in which the effects of 600 mg. of DMCT and 1 g. of TC daily for five days were compared, assays of the antibiotic content of faeces showed them to contain an average of 339 (range <60–600) μg./g. of DMCT and 1,196 (range 30–3,500) μg./g. of TC. This suggests that DMCT was better absorbed than TC. That the drug in the faeces is largely unabsorbed and not present owing to biliary excretion was suggested by the finding of little or no antibiotic in the faeces of subjects given TC intramuscularly. Observations by Sweeney, Dornbush, and Hardy[38] show considerable individual variation in the absorption of DMCT, which probably applies to all tetracyclines. About 5% of individuals regularly absorb these drugs poorly, the amount in the faeces then varying inversely with serum levels and with the amount recoverable in the urine.

Effect on Experimental Infections

Kuck and Redin[32] compared the therapeutic activity of TC and DMCT in several mouse infections. When the drug was added to the diet DMCT was nearly twice as effective against a staphylococcal infection, not only with respect to the plasma concentration required for equal therapeutic effects, but in terms of the oral dose needed to maintain the therapeutic plasma level. Against infections with *Str. pyogenes* or pneumococcus, approximately equal plasma concentrations and equal doses were required for comparable effects. Against a *Klebsiella pneumoniae* infection, DMCT and TC were equally active with respect to the plasma concentrations required for therapeutic effect, but twice as much TC was required to achieve the higher plasma levels needed to control this infection. In several series of tests of the effect of single subcutaneous doses DMCT was usually superior, evidently owing mainly to its more prolonged action: that it gives more persistent plasma levels in mice as in other animal species was verified.

*This activity is measured against *B. cereus*. The factors by which the activity of DMCT exceeded that of TC against the three organisms used in these assays were *B. cereus* 3.1, *Str. pyogenes* 2.2, and *Staph. aureus* 1.5.

Clinical Results

Clinical reports with varying amounts of detail are available about the effect of DMCT in pneumonias,[24 39] infections of the urinary tract,[25 31] brucellosis,[42] genital infections,[40] pustular dermatoses,[43] and amoebiasis[41]; others unpublished refer to surgical infections. Results have also been reported in a wide variety of medical diseases for which tetracyclines have been used in the past (Lichter *et al.*,[44] Fujii *et al.*,[37] Finland *et al.*[45]): the two last-named papers include results obtained at the same time with TC in similar cases. The numbers of patients varied from 9 to 169, and they were treated for periods varying from one day to several weeks with daily doses of 0.5–2 g. and individual doses of 125 mg.–1 g., sometimes with a larger initial loading dose.

With one exception, that of Elsdon-Dew *et al.*,[41] who got poorer results in amoebiasis than with other tetracyclines, these reports conclude that DMCT is as effective as TC and other tetracyclines in the whole range of infections for which these drugs have been used, but it has also been found in most of these studies that a smaller dose of DMCT has an equivalent effect. It is difficult to make a significant comparison between two such similar drugs, and the conclusion just stated may not be adequately based on any single one of these studies, but a consensus of opinion tallying with what is to be expected from the ascertainable properties of DMCT may be accepted with some assurance.

Untoward Effects

The tetracyclines have no serious toxicity unless given in excessive doses, and DMCT appears to be no exception. Its liability to cause diarrhoea is slight if moderate doses are given: whether it is greater than that of the other tetracyclines from larger doses only further experience can finally decide. Perry *et al.*[24] saw no untoward effects in 18 patients given 300 mg. twice daily, but nausea or vomiting occurred in 11 (38%) out of 29 patients given this dose four times a day. Lichter *et al.*[44] observed such disturbance in 2 out of 126 patients given up to 600 mg. daily, in 3 out of 12 given 1 g., and in 11 out of 18 given 2 g. Finland *et al.*,[45] in a simultaneous comparison, found that when DMCT was given in 50–60% of the dose of TC, the latter caused rather more gastro-intestinal side-effects. Garrod and Waterworth,[17] in a cross-over study in 48 normal subjects given 600 mg. of DMCT and 1 g. of TC, observed equal frequencies and degrees of mild disturbance in both groups (average 1.4 bowel actions daily in each).

An exaggerated sunburn reaction in patients being given DMCT has been recorded. In a case described by Morris[46] from the seaside resort of Corpus Christi, Texas, exposure to bright sunlight on the fifth day of treatment with 600 mg. of DMCT daily caused severe sunburn of exposed surfaces, with high fever, eosinophilia, and increased blood platelets. Deliberate attempts to reproduce this effect, about which we have had personal communications, were successful in Philadelphia in September and in Oklahoma in October: similar experiments with TC gave negative results. Four further instances are reported by Falk[47] among 27 ambulatory patients treated in Reno, Nevada. Carey[48] reports that only 40 patients among 2,682 treated with DMCT have exhibited this phototoxic reaction or anything which resembled it. It occurs only on skin exposed to sunlight containing rays in the range 2,700–3,200 Å: these are filtered out by ordinary window glass, and exist in the sunlight of temperate zones only in the summer. The reaction is not one of hypersensitivity, but a true phototoxicity, an important distinction as recently noted by Harber *et al.*[49] in connexion with a similar reaction to chlorothiazide.

Discussion

The tetracyclines have the broadest spectrum of all the antibiotics, ranging from the rickettsias and such viruses as are susceptible to chemotherapy through all the pyogenic cocci to the majority of the various Gram-negative bacilli, including the intestinal group and such others as *Brucella* and *Haemophilus*. There are many infections of the air passages, alimentary tract, urinary tract, and skin in which their use is appropriate, particularly if the bacterial cause has been identified and its sensitivity to the antibiotic verified.

We are concerned here with the relative merits of a group now including four substances. A natural first reaction must be one of astonishment that a change involving only one, two, or four atoms in a large molecule should have such a variety of effects on pharmacological behaviour and on antibacterial activity. There is a long way to go in relating structure with biological activity before the effects of these small changes can be explained. Nevertheless they are facts; a discriminating physician aware of them can choose a tetracycline for a specific purpose, and there are purposes for which each of them could rightly be chosen. We do not suggest that this is often done: the position until the advent of DMCT was that TC was preferred because it is better tolerated, and few physicians would have felt themselves seriously hampered if CTC and OTC had ceased to be obtainable.

We do not suggest that the relative merits of DMCT can yet be finally assessed, but it has several well-ascertained advantages. Its activity against many bacteria exceeds that of TC by a factor of about 2, and is perhaps approximately equal to that of CTC, but here comparison is difficult because CTC is so unstable that the result of a test depends largely on the length of the incubation period. By contrast, DMCT is exceedingly stable. It is perhaps better absorbed, although this requires further proof. What is quite certain is that it is much more slowly excreted, with the result that after the first few hours, during which its level in the blood is below that of TC although higher than that of OTC or CTC, it sustains an adequate level in the blood for much longer than any of the other three. This statement refers to actual concentrations: in terms of activity against many bacteria its superiority is even more striking.

Two conclusions are justified by these facts. It may confidently be said of DMCT that only two daily doses are required: the elimination of any need for six-hourly schedules of administration is an important advantage for patients who need, among other things, sleep. Out-patients are also less likely to miss a dose if it is to be taken only before breakfast and supper. Secondly, owing also to its greater antibacterial activity DMCT gives an equivalent therapeutic effect from a smaller dose than TC. Alternatively, an equal dose of DMCT is more likely to achieve the desired effect. These are very solid advantages, and, unless there are drawbacks of equal weight to set against them, DMCT may prove to be the preferred tetracycline of the future.

One drawback, certainly not of much consequence in ordinary circumstances, is the phototoxic reaction already described. The only other which has come to light, the importance of which has not yet been

measured, is the gastro-intestinal disturbance produced by larger doses. How far, if at all, this exceeds that produced by TC remains to be determined by further experience. This kind of tetracycline diarrhoea—as distinct from the much severer form due to infection of the gut by resistant staphylococci—deserves further investigation, and if some means could be found of overcoming it without interfering with the absorption of the drug all tetracycline therapy would be facilitated. Is it a chemical effect on the bowel mucosa or on the bowel contents, or does it operate through disturbance of the balance of the intestinal flora ? Is it promoted by relatively poor absorption and thus a higher concentration of the drug in the bowel ? If answers could be found to these questions, this nuisance factor might cease to operate in the choice between one tetracycline and another, or between tetracyclines generally and other drugs.

Summary

This paper reviews all the existing literature on demethylchlortetracycline (DMCT) and the results of other unpublished studies.

The significant properties of DMCT are: (1) high stability ; (2) an activity against most bacteria exceeding that of tetracycline (TC) by approximately twofold ; and (3) a rate of renal excretion less than half that of TC, with the result that therapeutic concentrations are maintained in the blood for a much longer time after a dose.

It may be concluded from these facts that DMCT can be administered at longer intervals than other tetracyclines—two daily doses should suffice ; and that a smaller dose of DMCT than of TC should achieve an equivalent therapeutic effect.

Larger doses of DMCT are apt to cause diarrhoea : whether this liability exceeds that of TC is not certain.

A phototoxic reaction peculiar to DMCT may occur in treated patients exposed to bright sunlight.

We are indebted to Lederle Laboratories Ltd. for the supplies of DMCT (" declomycin," " ledermycin ") used in our own studies.

REFERENCES

1 Duggar, B. M., and others, *Ann. N.Y. Acad. Sci.*, 1948, **51**, 175-342.
2 Keefer, C. S., and others, ibid., 1950, **53**, 221-460.
3 Stephens, C. R., Conover, L. H., Hochstein, F. A., Regina, P. P., Pilgrim, F. J., Brunings, K. J., and Woodward, R. B., *J. Amer. chem. Soc.*, 1952, **74**, 4976.
4 Council on Pharmacy and Chemistry, *J. Amer. med. Ass.*, 1953, **151**, 1000.
5 Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M., and Finland, M., *Ann. intern. Med.*, 1951, **35**, 1175.
6 Womack, C. R., Jackson, G. G., Gocke, T. M., Kass, E. H., Haight, T. H., and Finland, M., *A.M.A. Arch. intern. Med.*, 1952, **89**, 240.
7 Janbon, M., Bertrand, L., Salvaing, J., and Labauge, R., *Montpellier méd.*, 1952, **41-42**, 300.
8 Dearing, W. H., and Heilman, F. R., *Proc. Mayo Clin.*, 1953, **28**, 121.
9 Finland, M., Grigsby, M. E., and Haight, T. H., *A.M.A. Arch. intern. Med.*, 1954, **93**, 23.
10 —— and Haight, T. H., ibid., 1953, **91**, 143.
11 Boothe, J. H., and others, *Antibiotics Annual, 1953-1954*, pp. 46-107.
12 Finland, M., Purcell, E. M., Wright, S. S., Love, B. D., jun., Mou, T. W., and Kass, E. H., *J. Amer. med. Ass.*, 1954, **154**, 561.
13 Love, B. D., jun., Wright, S. S., Purcell, E. M., Mou, T. W., and Finland, M., *Proc. Soc. exp. Biol. (N.Y.)*, 1954, **85**, 25.
14 English, A. R., P'An, S. Y., McBride, T. J., Gardocki, J. F., Van Halsema, G., and Wright, W. A., *Antibiotics Annual, 1953-1954*, p. 70.
15 Wright, S. S., and Finland, M., *Proc. Soc. exp. Biol. (N.Y.)*, 1954, **85**, 40.
16 Purcell, E. M., Wright, S. S., Mou, T. W., and Finland, M., ibid., 1954, **85**, 61.
17 Garrod, L. P., and Waterworth, P. M., *Antibiotics Annual, 1959-1960*, p. 440.
18 McCormick, J. R. D., Sjolander, N. O., Hirsch, U., Jensen, E. R., and Doerschuk, A. P., *J. Amer. chem. Soc.*, 1957, **79**, 4561.
19 Sweeney, W. M., Hardy, S. M., Dornbush, A. C., and Ruegsegger, J. M., *Antibiot. and Chemother.*, 1959, **9**, 13.
20 Kunin, C. M., and Finland, M., *New Engl. J. Med.*, 1958, **259**, 999.
21 Hirsch, H. A., and Finland, M., ibid., 1959, **260**, 1099.
22 —— —— *Amer. J. med. Sci.*, 1960, **239**, 288.
23 Olarte, J., *Antibiotics Annual, 1959-1960*, p. 383.
24 Perry, D. M., Hall, G. A., and Kirby, W. M. M., ibid., p. 409.
25 Roberts, M. S., Seneca, H., Lattimer, J. K., Milner, P., Peer, P., and Troc, O. K., ibid., p. 424.
26 Vineyard, J. P., Hogan, J., and Sanford, J. P., ibid., p. 401.
27 Dornbush, A. C., and Pelcak, E. J., *Antibiot. and Chemother.*, in press.
28 Knothe, H., *Antibiot. Med. Brit. Ed.*, in press.
29 Clapper, W. B., and Proper, R., ibid., in press.
30 Lichter, E. A., and Gobel, S., ibid., 1960, **7**, 165.
31 Tunevall, G., and Frisk, A. R., ibid., 1960, **7**, 306.
32 Kuck, N. A., and Redin, G. S., *J. Pharmacol. exp. Ther.*, in press.
33 Kunin, C. M., Dornbush, A. C., and Finland, M., *J. clin. Invest.*, 1959, **38**, 1950.
34 —— and Finland, M., *New Engl. J. Med.*, 1959, **261**, 1069.
35 Boger, W. P., and Gavin, J. J., *Antibiotics Annual, 1959-1960*, p. 393.
36 Ross, S., Puig, J. R., and Zaremba, E. A., ibid., p. 388.
37 Fujii, R., Ichihashi, H., Minamitani, M., Konno, M., and Ishibashi, T., ibid., p. 433.
38 Sweeney, W. M., Dornbush, A. C., and Hardy, S. M., *New Engl. J. Med.*, in press.
39 Duke, C. J., Katz, S., and Donohoe, R. F., *Antibiotics Annual, 1959-1960*, p. 417.
40 Marmell, M., and Prigot, A., ibid., p. 457.
41 Elsdon-Dew, R., Wilmot, A. J., and Powell, S. J., ibid., p. 829.
42 Chavez Max, G., ibid., p. 429.
43 Kanof, N. B., and Blau, S., ibid., p. 660.
44 Lichter, E. A., Sobel, S., Spies, H. W., Lepper, M. H., and Dowling, H. F., *A.M.A. Arch. intern. Med.*, 1960, **105**, 601.
45 Finland, M., Hirsch, H. A., and Kunin, C. M., *Antibiotics Annual, 1959-1960*, p. 375.
46 Morris, W. E., *J. Amer. med. Ass.*, 1960, **172**, 1156.
47 Falk, M. S., ibid., 1960, **172**, 1156.
48 Carey, B. W., *Canad. med. Ass. J.*, 1960, **82**, 334.
49 Harber, L. C., Lashinsky, A. M., and Baer, R. L., *New Engl. J. Med.*, 1959, **261**, 1378.

STEATORRHOEA IN THE ADULT*

BY

J. BADENOCH, D.M., F.R.C.P.

Consultant Physician, United Oxford Hospitals

In this lecture I propose to survey the causes of steatorrhoea, and to consider the differential diagnosis and treatment of the malabsorption syndromes.

The pathogenesis of steatorrhoea is a very large subject and the number of conditions that can give rise to it is formidable. For this reason I shall deal with them in tabulated form and select from the list, for closer scrutiny, the subjects in which recent advances have been made, or on which further work is needed.

Group 1

Coeliac Disease. Idiopathic Steatorrhoea. Tropical Sprue

Until a short time ago the only justification for grouping these three together was that the cause of each was unknown.

It is possible, as Adlersberg (1957) believes, that all are due to a constitutional genetic defect which is unmasked by a number of different trigger mechanisms. In the case of coeliac disease and idiopathic steatorrhoea at least, the evidence for a common genetic background is quite strong. Cooke, Peeney, and Hawkins (1953) noted that many of their adult patients seemed to conform to a particular somatic type. Other workers, who

*The second of two Goulstonian Lectures delivered before the Royal College of Physicians of London on January 19 and 21, 1960. The first was published in last week's *Journal*.