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CHLOROMYCETIN

The latest antibiotic to gain a place in the chemotherapy of disease is chloromycetin, which was originally obtained from a streptomyces found in the soil of a field near Caraças, Venezuela, by Ehrlich and his colleagues[1]; it has now also been isolated from a streptomyces found in a compost heap in Illinois.[2] A preliminary examination of the antibiotic activity of chloromycetin by Smadel and Jackson[3] showed that in addition to having some action on viruses of the psittacosis-lymphogranuloma group it inhibited the growth of a number of pathogenic rickettsiae both in experimental animals and in developing chick embryos. Chloromycetin is active when given by mouth, and Ley and his co-workers[4] showed that a dose of 1.0 g. by mouth daily for 11 days caused no abnormal signs or symptoms. The substance is found in the greatest quantity in both blood and urine two hours after an initial dose of 1.0 g. by mouth, the estimation being carried out by a method of microbiological assay which involves inhibition of the growth of *Shigella paradysenteriae* (Sonne). After two hours the blood levels steadily fall from about 6 μg. per ml. till at eight hours detectable amounts are no longer found. Urine levels of the drug are approximately 200 μg. at two hours, falling to 50 μg. per ml. at eight hours and remaining at this level for the next 10 days of treatment. When an initial dose of 2.0 g. of chloromycetin is given blood levels are 10 μg. per ml. at two hours and above 5 μg. at the end of eight hours. Urine levels are highest at two hours, reaching values of 380 and 670 μg. per ml. and falling to about 10 μg. per ml. at eight hours. The fact that appreciable amounts of chloromycetin are found in blood and urine 30 minutes after being given by mouth indicates that the antibiotic must be rapidly absorbed from the gastrointestinal tract. Approximately 10% of the total amount of chloromycetin given daily was recovered in active form in the urine of volunteers; much must therefore be metabolized. No signs or symptoms attributable to toxicity were observed in three volunteers during or after the treatment; examination of the blood and urine showed no abnormalities. Since the drug is rapidly excreted or inactivated its administration at fairly frequent intervals is obviously necessary.

The activity of chloromycetin and its lack of toxicity have been confirmed by Smadel and his colleagues,[5] who used it in the treatment of cases of typhus fever in Mexico. Three adults and one child were suffering from epidemic louse-borne typhus and one child from the murine type. One of the adults was very severely affected and was not treated till the seventh day of illness; then 1.5 g. was given by mouth, followed one hour later by 1.5 g. and thereafter 0.2 g. every two hours for four days and subsequently 0.2 g. every three hours for three days. The other two adults first treated on the fifth and sixth days of illness received an initial dose of 1.0 and 2.0 g. respectively, followed by 0.2 g. every four hours for the next three to four days. In the patient given the largest doses blood levels of 40.5 μg. per ml. and urinary levels of 400 μg. per ml. were attained; in the other patients the maximum blood levels were 5 and 11.5 μg. per ml. and the urinary levels 100 and 220 μg. per ml. The most noticeable result in all cases was the rapid fall in temperature while the rash remained unchanged. Results in the children were less easy to judge, since typhus in childhood is a comparatively mild disease. No toxic reactions due to the drug were observed. Though the best dosage can be determined only by much further study, it is suggested that the initial dose should be 40 mg. per kg. of body weight, followed by a total daily dosage of 35 mg. per kg. given in divided amounts at two-hourly intervals until obvious improvement in the general condition occurs. Thereafter 20 mg. per kg. of body weight should be given four-hourly till the thirteenth or fourteenth day after onset of the disease.

At present the effect of the drug on scrub typhus is being investigated in Malaya by an American team headed by Dr. J. E. Smadel, who is working in collaboration with Dr. Lewthwaite and Dr. Savoor at Kuala Lumpur. Preliminary results, which were announced at the International Congress of Tropical Medicine at Washington held in May of this year, are very encouraging. Twenty-five patients have so far received chloromycetin, and 12 patients from the same areas have been used as controls.

Among those treated none has died and no complications have developed. The duration of fever after the first dose averaged 31 hours and the whole febrile period 7.5 days. Among the untreated controls one died, and this patient and one other had serious complications; the mean duration of fever was 18.1 days. At first the same large doses were given as were thought to be necessary in louse-borne typhus, but gradually the dosage was reduced till only 6 g. was administered in 24 hours to the last seven patients. The results, however, were equally good. Half the patients were nursed under "bush" conditions in the hospitals attached to rubber estates. Further studies on the results of chloromycetin in rickettsial diseases will be awaited with great interest, for rickettsiae are resistant not only to the older chemotherapeutic arsenicals and antimonials but also to the sulphonamides and penicillin. Recent investigations by Smith and his colleagues[6] have shown that, though yeasts, fungi, protozoa, and viruses other than those of the psittacosis-lymphogranuloma group are unaffected, chloromycetin is active against a number of Gram-positive and Gram-negative bacteria, particularly Friedländer's bacillus, *Bacterium coli, Salmonella typhi, S. paratyphi, Shigella paradysenteriae* and *Haemophilus pertussis*. It is moderately active against various strains of tubercle bacilli. Bartz[7] has recently isolated chloromycetin in crystalline form. Its stability in solution is greater than

[1] *Science*, 1947, **106**, 417.
[2] Gottlieb, D., Bhattacharyya, P. K., Anderson, H. W., and Carter, H. E., *J. Bact.*, 1948, **55**, 409.
[3] *Science*, 1947, **106**, 418.
[4] *Proc. Soc. exp. Biol., N.Y.*, 1948, **68**, 9.
[5] Ibid., 1948, **68**, 12.
[6] *J. Bact.*, 1948, **55**, 425.
[7] *J. biol. Chem.*, 1948, **172**, 445.

that of penicillin and in the acid range greater than that of streptomycin. It can be heated to 100° C. for five hours without loss of activity. The solubility of the pure product in water is rather low, only 2.5 mg. per ml., but its solubility in pure propylene glycol is high. When given parenterally it causes considerable irritation, but as it is extremely active when taken by mouth this is not of great importance. Another antibiotic of the same type, auromycetin, has now been isolated; preliminary reports suggest that it, too, is active against rickettsiae.

FORMATION OF ADRENALINE AND HYPERTENSION

It is not yet known how adrenaline is formed in the body, but information is steadily accumulating. The general conception of the breakdown of amino-acids in the body was that they first lost their amino group in the process of oxidative deamination. In 1938 Holtz, Heise, and Lüdtke[1] found an enzyme in various tissues capable of removing the $-COOH$ group from dihydroxyphenylalanine (dopa), and they suggested that such an enzyme might play a part in the general breakdown of amino-acids, which only lost the amine group after decarboxylation. Blaschko[2] showed, however, that the enzyme discovered by Holtz and his colleagues was specific for dopa, and other amino-acids were not decarboxylated; thus the process was evidently not a general one. The question then arose why dopa decarboxylase should exist, and Blaschko[3] suggested that it was probably concerned in the formation of adrenaline from tyrosine. The first change might be the introduction of a second phenolic hydroxyl group into the tyrosine molecule, thus forming dopa. Decarboxylation would then give hydroxytyramine, though whether the introduction of an $-OH$ group into the side chain occurred before or after this decarboxylation there was at that time no means of knowing. Blaschko, however, showed that N-methyl dopa was not decarboxylated, and concluded that the primary amine noradrenaline must be formed as a preliminary to the formation of adrenaline itself.

The next step followed Holtz and Credner's[4] important observation that when dopa was given by intravenous injection or by mouth to rabbits a pressor substance appeared in the urine which they were able to identify chemically as hydroxytyramine. Thus they produced evidence of the normal activity in the body of the dopa decarboxylase. In the course of further work, Holtz, Credner, and Kroneberg[5] have shown that in normal urine there are pressor substances which are set free after acid hydrolysis, and they have produced pharmacological evidence which strongly suggests that these are a mixture of hydroxytyramine, noradrenaline, and adrenaline. They think that these substances may be produced in excess in the process of adrenaline formation, and that the body then gets rid of them in inactive forms which are excreted in the urine. They call the mixture urosympathin. They find that the amount of these substances in the urine is increased in healthy individuals after strenuous exercise, and also in patients suffering from essential hypertension. In normal individuals the amount of urosympathin excreted in 24 hours is equivalent to 2–3 mg. of hydroxytyramine, or to 0.1–0.15 mg. of adrenaline. In essential hypertension it is equivalent to 8 mg. of hydroxytyramine.

In a further paper Holtz and Credner[6] point out that renal ischaemia, by reducing the oxygen supply, will inactivate another enzyme which probably plays a part in removing substances like hydroxytyramine, which may be formed in excess. This is the enzyme amine oxidase, which converts hydroxytyramine to dihydroxyphenylacetaldehyde. The inactivation of amine oxidase will raise the amount of pressor amines in the blood. Loss of excretory power may have the same effect. Holtz and Credner administered 50 mg. of L-dopa intravenously to 14 patients with nephritis and high blood pressure and also to 8 healthy subjects; they tested the urine excreted in the following 2–4 hours for the presence of hydroxytyramine by its effect on the blood pressure of the cat. They found little or no hydroxytyramine in the urine of the patients with nephritis and high blood pressure, but considerable amounts in that of the normal subjects. They demonstrated that the absence of hydroxytyramine in the patients' urine was not due to failure to convert the dopa to hydroxytyramine, for they found no dopa in the urine when they tested it for the total amount of polyphenol compounds. Thus renal ischaemia may lead to over-production of pressor amines by inactivation of amine oxidase and also to their retention in the blood. It should be made clear that these observations are considered by the authors to represent a subsidiary cause of hypertension, of less importance than the action of renin on hypertensinogen.

It has been shown by Blaschko, Holton, and Sloane Stanley[7] that in the formation of adrenaline the introduction of the $-OH$ group into the side chain must follow decarboxylation, since they have found that the carboxylic acid of noradrenaline is not decarboxylated in animal tissues. This agrees with Holtz's evidence that dopa gives rise in the body to hydroxytyramine. Finally, Holton's[8] recent observation that a suprarenal medullary tumour, taken from a patient who suffered from temporary crises of hypertension, contained about twice as much noradrenaline as adrenaline supports the view that the last stage of adrenaline formation is the N-methylation of noradrenaline.

[1] *Arch. exp. Path. Pharmak.*, 1938, **191**, 87.
[2] *J. Physiol.*, 1939, **96**, 50P.
[3] Ibid, 1942, **101**, 337.
[4] *Arch. exp. Path. Pharmak.*, 1942, **200**, 356.
[5] Ibid., 1947, **204**, 228.
[6] Ibid., 1947, **204**, 244.
[7] Communication to Biochemical Society, March 12, 1948.
[8] Communication to Physiological Society, May 21, 1948.

END OF RADIUM COMMISSION

The affairs of the National Radium Trust and the Radium Commission are being wound up as a result of the coming into force of the National Health Act. The two bodies were established by royal charter issued under letters patent of July 25, 1929. The functions of the Trust were primarily to augment the supply of radium, and later, by supplemental charter, other radiotherapeutic apparatus, for use "in relation to the treatment of the sick in Great Britain" and for "the advancement of knowledge of the best methods of rendering such treatment." The main duty of the Commission was "to make arrangements for the proper custody, equitable distribution, and full use of the radium . . . of the Trust with the object of promoting the