or leukaemias in mice and rats, however, was rather limited. DMBA-induced skin carcinomata in mice regressed in response to treatment with 250 mg/kg p.o. daily for 10 days.

Rats with DMBA-induced tumours tolerated the compound well. From the second week of treatment onwards, slight weightloss concurrent with reduced food consumption was noted. Four and 7 days, respectively, after treatment was with-drawn, food intake and weight-gain reverted to normal. Apart from a reduction in the size of the uterus, no abnormalities were observed upon macroscopic examination of the treated rats. Microscopically, increased lymphopoiesis was noted in the spleen. There were no changes in the white blood cell counts.

The median lethal oral and subcutaneous doses (LD_{50}) of GP 48 989 in rats and mice were greater than 5000 mg/kg. In view of its promising carcinostatic activity, GP 48 989 appears to merit thorough clinical investigation.

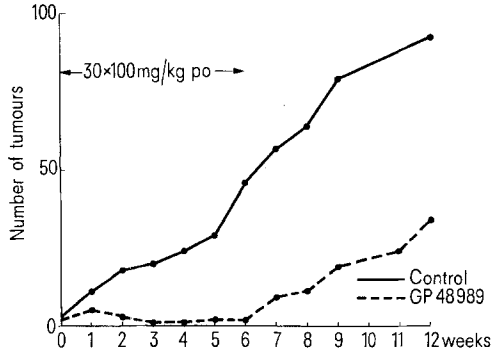

Fig. 1. Inhibition of the appearance of DMBA-induced mammary tumours in rats treated with GP 48 989.

Zusammenfassung. 5-Methyl-3-(2-methylallyl)-2-[(3-methyl-4-oxo-2-thiazolidinyliden)-hydrazono]-4-thiazolidinon erwies sich bei guter therapeutischer Breite als stark karzinostatisch wirksam bei DMBA-induzierten Mamma-Karzinomen weiblicher Sprague-Dawley Ratten. Eine geringere chemotherapeutische Wirkung fand sich auch bei Walker CaSa 256, DMBA-induzierten Hautkarzinomen und Ehrlich Ascites Karzinom.

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Cannabidiol and Cannabinol in Man

Evidence is rapidly accumulating that the major source of pharmacological activity of cannabis is due to Δ-9-tetrahydrocannabinol (THC) or its metabolites[1-3]. Although the Δ-8-THC isomer, normally a minor component of cannabis, is also active, its effects in man are qualitatively identical to those of the Δ-9-THC and only two-thirds as potent[4]. 2 other major cannabis constituents, cannabidiol (CBD) and cannabinol (CBN), have been considered to be inactive on the basis of animal studies. (Figure 1) Both these cannabinoids, as well as cannabichromene, cannabigerol and cannabicyclol were found to be inactive in monkeys, and did not alter the response of these animals to doses of Δ-9-THC given concurrently[5]. CBN in doses up to 180 mg/kg had no effect on key pecking of pigeons trained in an operant schedule[6]. As the possibility always exists that compounds may be metabolized differently in man than in other species, and that some found to be inactive in the latter may be active in man, both CBD and CBN were tested in volunteer subjects.

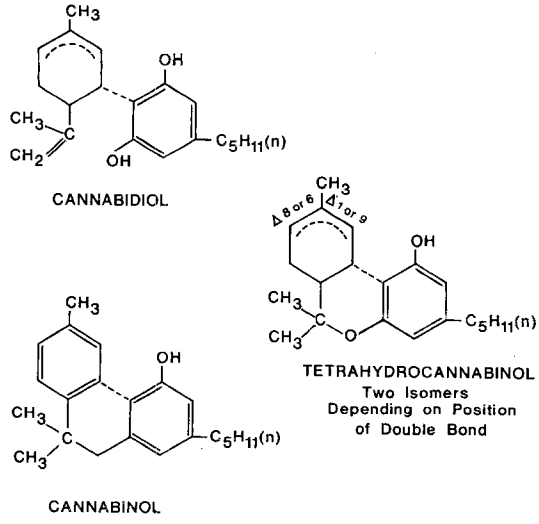

Fig. 1. Structural relationships between 3 major cannabinoids. The biosynthetic pathway is presumed to be from cannabidiol to tetrahydrocannabinol to cannabinol.

Methods and materials. The volunteer subjects were men, mostly in the 3rd and 4th decades of life. All had some prior experience with marihuana, and some with other pure cannabinoids, but none were more than casual social users of the drug. CBN and CBD were administered orally by laying an ethanolic solution of the drugs on chocolate cookies and then evaporating the solvent under nitrogen. This technique has been successfully employed in administering oral doses of THC. 6 subjects received oral doses of CBN ranging from 20 to 400 mg. 5 subjects received oral doses of CBD, ranging from 20 to 100 mg. CBD was given i.v. as well, the ethanolic solution being injected into a rapidly flowing stream of saline. 4 subjects received i.v. doses of CBD ranging from 5 to 30 mg. This technique has allowed i.v. injection of pharmacologically

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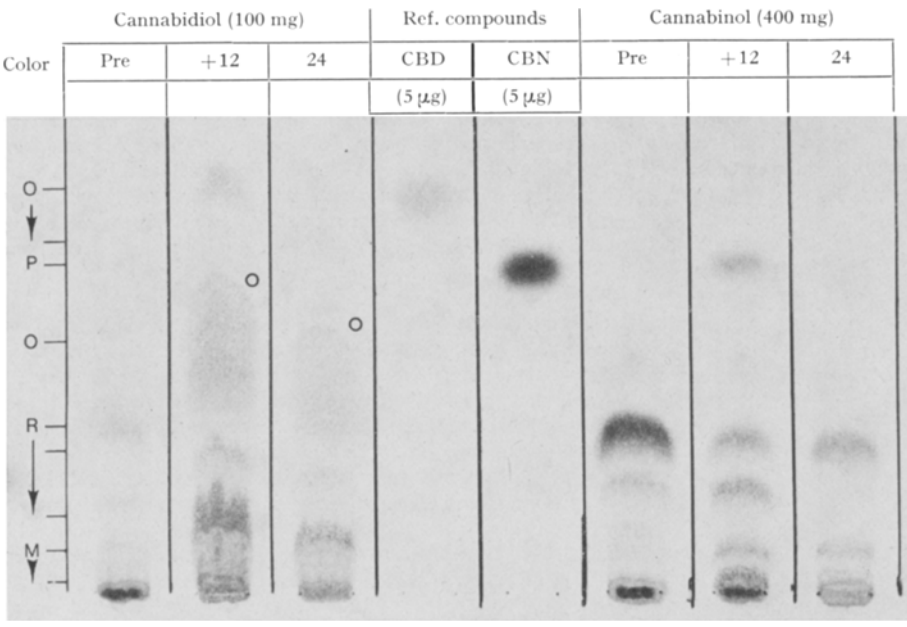

Fig. 2. Thin-layer plate of urine fractions prior to treatment and during the first and second 12-h periods after oral doses of 100 mg of CBD and 400 mg of CBN. Note presence of unchanged CBD and CBN during the first 12 h as well as appearance of new spots of a slower-moving, more polar type. Abbreviations: O, orange; P, purple; R, red; M, magenta coloring of spots.

active doses of both THC isomers and their metabolites to man. Because CBN is less compatible than CBD with any aqueous medium, this route of administration was not used for this substance.

Results. Oral doses of CBD and CBN started with 10 mg, a dose of THC usually showing definite, though moderate clinical effects in man. At no oral dose level were any of the characteristic mental or physical effects of THC observed. Urine samples taken from the subjects receiving the maximum oral doses were subjected to thin-layer chromatography, using techniques previously described[7]. Both CBD and CBN, unlike THC, were excreted in part unchanged. (Figure 2) Other metabolites related to their intake were also observed as new spots on the chromatograms. The initial i.v. injection of CBD was 5 mg; an equal dose of THC produces a strong and lasting effect by this route. As no reaction was noted, larger doses were subsequently used (10, 20 and 30 mg). None of the characteristic mental effects of cannabis were observed, as well as a complete absence of any change in pulse rate or degree of conjunctival reddening.

Discussion. The inactivity of these cannabinoids has been confirmed in man. In part, this difference from THC may be due to a somewhat different metabolism of CBD and CBN. It is still possible that these cannabinoids, although inactive themselves, might interact with THC to alter its effects. CBN pretreatment antagonized the prolongation of sodium pentobarbital sleeping time produced by THC in mice[8]. CBD inhibited not only the metabolism of THC but also that of tis primary metabolite, 11-hydroxy-THC, a compound with at least the same degree of activity as THC itself. Thus, CBD might enhance the effects of THC without having direct THC-like actions. As the assertion is often made, and widely believed, that different types of cannabis have different patterns of pharmacological effects independent of differences in THC content, such interactions might still afford an explanation for such differences. These differences cannot be attributed to direct pharmacological effects of CBD or CBN themselves.

Résumé. Le cannabidiol administré à dose de 100 mg par os et de 30 mg par injection i.v. fut inactif dans les sujets d'étude. Le cannabinol, à dose orale de 400 mg, le fut aussi. Ces constituants du cannabis ne contribuent donc pas à l'effet pharmacologique.

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The Effect of Pentobarbital on Brain 5-HT Metabolism in Mice

BONNYCASTLE, GIARMAN and PAASONEN[1] observed an increase of brain serotonin (5-HT) concentration after i.p. injection of pentobarbital in rats. It seemed of interest to us to investigate whether this increase was due to an accelerated synthesis or a decreased metabolism of 5-HT.

Materials and methods. Male NMRI/Han mice of 25–35 g were kept in groups of 10 at room temperature (20–22 °C) on an ad libitum diet of food and water. The mice were killed by decapitation. The brains were kept in 96% ethanol for 30–60 min. This treatment was without influence upon brain serotonin concentration. The neo-

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