tion: $K = -0{,}00037\ C - 0{,}0174$ où sont représentés: l'index phagocytaire: K, la dose de carbaryl administrée: C, la pente de la droite: $-0{,}00037 \pm 0{,}00006$, l'index phagocytaire lorsque l'administration de carbaryl est nulle: $-0{,}0174 \pm 0{,}0003$. L'étude statistique de la pente de cette droite (test de t) montre que la variation de l'index phagocytaire est fonction de la dose de carbaryl administrée ($t = 6$; $p < 0{,}001$). La comparaison des variances entre les doses de carbaryl et de la variance totale des données montre que la droite de régression est bien linéaire ($F = 0{,}65 < F^{1}_{35}$ à 5%). Ainsi, dans nos conditions expérimentales, il y a une relation linéaire entre la dose de carbaryl administrée et l'inhibition de la phagocytose observée 1 h après traitement. Le carbaryl semble donc avoir un impact sur les cellules du SRE et notamment sur les cellules de Küpffer du foie responsables à elles seules de 80–90% de l'épuration sanguine du carbone colloïdal[8]. Cette diminution progressive de la phagocytose en fonction de la dose administrée laisse supposer que le carbaryl, substance anticholinestérasique, pourrait être responsable de l'inhibition de sérine estérases pouvant jouer un rôle dans les processus membranaires accompagnant la phagocytose[4]. Ce résultat peut être rapproché de l'inhibition de la phagocytose des globules rouges par des leucocytes en présence d'inhibiteurs de la sérine estérase[3] où l'intensité de l'inhibition est également fonction de la dose. La diminution progressive de la vitesse de phagocytose du carbone colloïdal pourrait être également le résultat d'une compétition croissante entre les particules de carbaryl que nous avons administrées en fine suspension et le carbone colloïdal. Un tel mécanisme a été montré lorsque le carbone colloïdal et une autre substance particulaire se trouvent en compétition pour les sites membranaires des macrophages[9]. Des études plus approfondies seraient nécessaires pour élucider la cause de cette inhibition et les mécanismes membranaires régissant la phagocytose. Connaissant l'importance de la fonction phagocytaire des macrophages du SRE dans la défense de l'organisme, il serait en effet important de préciser ces faits surtout lorsqu'on sait que le carbaryl, présent dans l'environnement, peut être absorbé en tant que résidu dans les aliments ou être en contact cutané accidentel[10].

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Different effects of synthetic Δ^9-tetrahydrocannabinol and cannabis extract on steroid metabolism in male rats[1]

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Summary. Repeated oral administration of cannabis extract as well as synthetic Δ^9-tetrahydrocannabinol to male rats produced significant changes in excretion of androgenic steroids and their metabolites as detectable in blood and urine. Cannabis extracts were found to be significantly more active than the mixtures containing same amounts of synthetic cannabinoids.

There have been conflicting reports[3–5] on cannabis affecting the normal reproductive ability of human males. Studies with rodents, using greater amounts of cannabis resin or synthetic Δ^9-tetrahydrocannabinol (THC), have presented a more conclusive evidence for reduced copulatory behavior[6,7], growth inhibition[8,9] and a retarded development of testes, seminal vesicles, and prostate[8,10,11]. Significant accumulation of the radioactive THC in rat testes has also been noted[12]. Since the 'demasculinizing factor' of cannabis does not appear to have directly an estrogenic activity[11], a complex mechanism of altered steroidal pathways appears to be involved. Detailed biochemical studies can potentially elucidate the consequences of administration of the drug. During the course of such studies[13], we have observed that the alteration in the excretion of steroids is significantly different for cannabis extracts as compared to synthetic THC. Such differences were observed with both urinary and plasma steroids.

Materials and methods. Male Wistar rats (100–200 days old) weighing 300–450 g were orally administered for 7 days either the extract of Mexican cannabis or synthetic THC (doses corresponding up to 50 mg/kg of THC) using propylene glycol as the vehicle, with controls given vehicle only. All drugs were obtained from the National Institute on Drug Abuse, Rockville, Maryland. The animals were first allowed to acclimate themselves in the metabolism cages for 3 days. As a rule, 4 animals were used in each experiment, but the described experiments were repeated at least 3 times with quite reproducible results. Urine samples were collected (total of 11 daily collections) over dry ice and kept frozen until analyzed. Venous blood

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(typically, 5 ml) was collected from the tail, using EDTA as an anticoagulant. Animals were bled at the end of the 7th day (bleeding consistently done at the end of daytime period, at 20.00, to minimize daily fluctuation in hormone levels), and urine was not collected during a 24-h-period following blood collection.

Urinary steroids were isolated by a combination of the procedures of Horning and Horning[14] and Luyten[15] and the profiles of their volatile derivatives recorded by high-resolution gas chromatography using a 20 m × 0.28 mm, ID, glass capillary column coated with GE SE-30 silicone gum stationary phase. Plasma steroids were isolated and analyzed by the gas-chromatographic method developed in our laboratory[16]. The identity of studied compounds was verified by means of a combined gas chromatograph/mass spectrometer (Hewlett-Packard Model 5980 A) and through chromatographic retention of authentic samples. Testosterone was determined by means of electron capture detector as its methoxime-heptafluorobutyryl derivative.

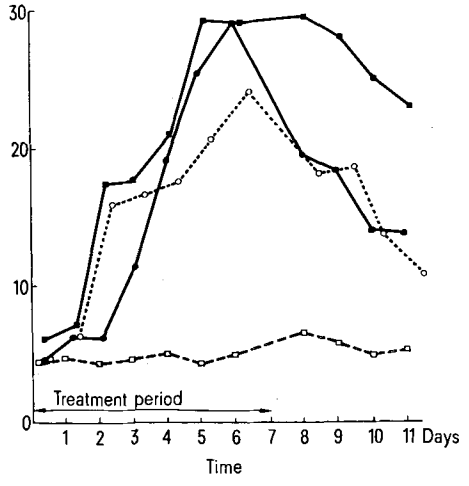
Results and discussion. The normal concentrations of testosterone in rat plasma were found to be 452 ± 38 ng/100 ml (an average of 11 determinations). The values are somewhat higher than those obtained for male rats by means of a radioimmunoassay procedure and reported by Gupta et al.[17]. Whereas testosterone was unaltered by THC administration except for the relatively high dose of 50 mg/kg, the rats given already 5 mg/kg of the cannabis extract showed significant (99.9% confidence using t-distribution) decrease of testosterone concentration. A mixture of the main synthetic cannabinoids (THC, 10.0 mg/kg; cannabinol (CBN), 3.4 mg/kg; and cannabidiol (CBD), 7.8 mg/kg in a single dose) blended to simulate the cannabinoid content of the used cannabis extract failed to produce any substantial decrease of testosterone.

One of the major urinary steroids that was identified through its mass spectrum and chromatographic retention as Δ^{16}-androstene-3β-ol, showed marked dose-response related elevation in rats given THC. However, this elevation is even more pronounced after the daily administration of cannabis extract (figure). It should be noted that testosterone can be considered a likely precursor of this steroid. In a similar fashion, a 3fold increase of androstanediol concentration over the control was found following the administration of cannabis as contrasted by approximately 1.5 times increase due to synthetic THC. According to Matsui et al.[18], 5α-androstene-3β, 17β-diol is the major metabolite of testosterone sulfate found in male rat bile. Again, none of the observed differences could be attributed to the other major cannabinoids. Elevation of urinary androsterone (from approximately 10 for controls to 80 µg/24 h) for THC-treated and cannabis-treated rats was not significantly different. Also, a trace amount of etiocholanolone that is adjacent to the androsterone chromatographic peak dropped below its detection limit after the treatment of rats with both THC and cannabis extract. Although the analyses of plasma conjugated steroids following a complicated extraction and fractionation scheme[16] have to be considered less accurate than those of urinary steroids, markedly increased Δ^{16}-androstenol monosulfate and androstanediol disulfate were consistently observed; again, this effect was more pronounced in cannabis-treated as compared to THC-treated rats.

Although the mechanism of drug interference with the normal gonadal and adrenal metabolism has yet to be investigated in detail, the presented results strongly indicate that the actions of synthetic THC and cannabis resin are not synonymous. Whereas this may not be hard to understand in view of the many hitherto unidentified cannabis constituents, it should be cautioned that majority of related endocrinological studies are usually performed with synthetic THC preparations. Since the remaining major cannabinoids of the used extract were not found responsible for the enhanced effects, other cannabis constituents must be considered. Our preliminary studies have also ruled out olivetol that was previously found active as an inhibitor of prostaglandin synthetase[19].

Testosterone levels in marijuana treated rats

Dosage regimen	Plasma testosterone level ± 1 SD
Control (11 animals)	452 ng/ml ± 37.7
1 mg/kg THC	472 ng/ml ± 35.0
5 mg/kg THC	443 ng/ml ± 39.8
10 mg/kg THC	467 ng/ml ± 45.0
25 mg/kg THC	427 ng/ml ± 36.3
50 mg/kg THC	361 ng/ml ± 23.6
5 mg/kg THC in cannabis extract	345 ng/ml ± 29.8
10 mg/kg THC in cannabis extract	160 ng/ml ± 18.5
10 mg/kg THC + 7.8 mg/kg CBD + 3.4 mg/kg CBN	453 ng/ml ± 32.7



Excretion of Δ^{16}-androstenol due to the treatment of rats with the drug. □ control; ● 10 mg/kg THC; ○ 5 mg/kg THC in the cannabis extract; ■ 10 mg/kg THC in the cannabis extract.

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