some of the differences were of enough significance to warrant presentation at this time.

Female mice of the strains listed in the Table, obtained from the inbred stocks of the Detroit Institute of Cancer Research, were mated with their brothers and the progeny of the first, second, and third litters were sexed within 16 h after birth. Sexes were rechecked at least twice thereafter. Mating pens consisted of 1–4 females and 1 male. All mice were kept in wooden boxes, which were changed weekly, on racks in an air-conditioned room. Water and a commercial diet (Purina Laboratory Chow) were given *ad libitum*. When a female became detectably pregnant, she was isolated. She was returned to her original mate after her litter was weaned at 5 weeks or earlier if the litter died prior to weaning. As far as could be judged from carcasses, the number of stillbirths was estimated at less than 1%; and since it was difficult to sex the remains, they have been excluded from the data.

The results are presented in the Table. All data were analyzed statistically. Those involving the number of mice per litter were tested by Student's t-test; all others were analyzed by the Chi square method with Yates's correction for sample size.

The secondary sex ratio was elevated in all first litters but was significantly different from the theoretical value of 100 only in those born to C3H/Sp ($P < 0.05$), PL/Sp ($P < 0.01$), and AKR/Sp ($P < 0.02$) mothers. The ratio in second and third litters was invariably lower and not significantly different from the theoretical except in the case of third litters of MA/Sp mice ($P < 0.05$). The ratio was significantly decreased in second and third litters of C3H/Sp, $C3H_f$/Sp and PL/Sp mice ($P < 0.05$) from that found in first litters.

The decrease in the secondary sex ratio in succeeding litters could have been due to a decrease in the number of male births and/or an increase in female births. To elucidate this point the number of male and female births per litter were compared in those strains (C3H/Sp, $C3H_f$/Sp, and PL/Sp) that showed a significant decrease in the ratio. Significant increases in female births were found in second and third litters ($P$ was 0.01) of C3H/Sp mice. The increase in female births in third litters of $C3H_f$/Sp and PL/Sp mice was at the borderline of significance ($P$ was 0.05). No significant change in the number of male births was observed. These findings suggest that the increases in female live births played a role in the decrease of the secondary sex ratio in later litters of these strains. The data are contrary to the generally held idea that the decrease in the sex ratio at birth is due to a diminution in male births[5,6].

The deviation of the observed ratio from the theoretical value of 100 in first litters of C3H/Sp, PL/Sp, and AKR/Sp mice could be due to genetic and/or nongenetic factors. Mating of PL/Sp females with C57BL/Sp males (from a strain in which no deviation of the observed from the theoretical ratio was found) yielded first litter $F_1$ hybrids in which the ratio was 138. The latter did not significantly deviate from the theoretical. The reciprocal crosses yielded first litter progeny in which the ratio was 122. The latter did not significantly deviate either from the theoretical or from the actual ratio found in the first cross. The data for the first litter reciprocal $F_1$ hybrids were, therefore, pooled. The ratio of these pooled hybrids differed significantly from that of PL/Sp first litter mice ($P < 0.05$) but not from that of C57BL/Sp first litter progeny. These figures suggest that the apparent increase in the secondary sex ratio of first litter PL/Sp mice may be partially attributed to genetic factors. The decrease of the ratio in succeeding litters then implies a compensating nongenetic mechanism.

*Zusammenfassung.* Es wird gezeigt, dass sich verschiedene Mäusestämme im sekundären Geschlechterverhältnis unterscheiden. Die Wurffolge beeinflusst zwar die relative Zahl der Geschlechter bei der Geburt, aber dieser Einfluss wechselt mit dem Stamm selber. Der Ausgleich des Unterschieds in späteren Würfen erfolgt durch Weibchenüberschuss. Sowohl erbliche wie nichterbliche Faktoren spielen eine Rolle in der Beeinflussung des Geschlechterverhältnisses.

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## The Content of Acid Fraction in Cannabis Resin of Various Age and Provenance

Considerable interest has recently been focused on the alkali soluble part of cannabis resin. Although this fraction does not exhibit any marked hashish activity[1,2], it has been observed that such constituents readily become converted by heat or by long standing into biologically active cannabinolic compounds which are insoluble in aqueous alkali[1,3]. After the isolation of cannabidiolic acid from the alkali fraction of the resin[4,5], this constituent was believed to be precursor of other cannabinolic substances[6]. By decarboxylation it yields cannabidiol[6] which can be converted by intramolecular condensation into physiologically active tetrahydrocannabinols[7], the latter yielding by spontaneous dehydrogenation almost inactive cannabinol[8,9].

Although the process of formation of various constituents of cannabis resin seems to be a very complex one, cannabidiolic acid may be considered as the main initial constituent in the gradual conversion of cannabinolic compounds. Consequently, the stage of the conversion process in a given sample of cannabis may be expected to be roughly indicated by the approximate content of cannabidiolic acid in hemp resin. Such data might be of interest in approaching the problem of determining physiological potency, geographical origin and the age of the drug.

In order to obtain a picture of the approximate content of cannabidiolic acid in various types of hemp resin, the acid fraction of the resin extracted from 31 available

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samples of *Cannabis sativa* from 10 different countries has been determined. The procedure adopted was based on the experience of some previous authors[3,6]. The extract in petrol ether was shaken out with a solution containing 5% NaOH and 5% $Na_2SO_3$. The alkali extract obtained was acidified by means of diluted $H_2SO_4$, extracted with ether, dried in vacuum, weight and calculated as percentage in dry petrol ether extract. In order to avoid decarboxylation of cannabidiolic acid, the procedure has to be run rapidly. Duplicate analyses have indicated a good reproducibility of the results. Although the acid fraction obtained by this way might contain also some other weak acids, the results are treated as if they correspond only to the content of cannabidiolic acid, which is obviously the main constituent of this fraction. The results obtained are summarized in the Table.

As is seen, the content of acid fraction in resin ranged from 3.8% to 41.7%. It was lowest in cannabis originating in tropical regions, while highest in samples from European countries, marked in the Table as 'northern area'. Samples from Mediterranean area exhibited the properties of both the groups, mostly showing the tendency to an intermediate content of acid fraction. In spite of the lack of exact data dealing with the age of certain samples, some results show that there is a lower content of acid fraction in old resin than in fresh.

The results obtained indicate that the phytochemical process of gradual conversion of cannabinolic compounds ('ripening' of the resin) is rather advanced in varieties growing in hot regions. In contrast to this, in plants developed under unfavourable climatic conditions, the 'unripe' type of the resin predominates, containing a large amount of unchanged cannabidiolic acid. It seems probable that even fresh cannabis from tropical regions mostly belong to the 'ripe' type, as the largest part of acid is converted before harvesting to more thermostable products. However, such cannabis might still be exposed to a further slight decrease in acid content during storage. In 'unripe' type of the drug, originating from northern areas, the process of additional 'ripening' during storage seems also to occur under favourable conditions. According to the results obtained, it seems that the intermediate type, represented in our work by the samples from the Mediterranean area, exhibits the greatest variations in acid content, and is probably more affected by the time and conditions of storage than the two previous types. Some of the conclusions drawn here may confirm previous findings, based on direct ultraviolet spectrophotometry of cannabis resin[10,11].

The content of acid fraction in various groups of samples

| Origin Area | Country | Age (Production year) | Number of samples analyzed | Percentage of acid fraction in resin |
|---|---|---|---|---|
| Tropical | Burma | old | 1 | 3.8 |
| Tropical | Costa Rica | old | 1 | 7.0 |
| Tropical | Brazil | 1959 | 14 | 5.2–10.7 (mean 8.2) |
| Mediterranean | Greece | — | 5 | 8.9–15.4 (mean 12.0) |
| Mediterranean | Yugoslavia | — | 1 | 16.1 |
| Mediterranean | Morocco | 1960 | 1 | 18.5 |
| Mediterranean | Cyprus | old | 1 | 14.1 |
| Mediterranean | Cyprus | 1959 | 1 | 33.7 |
| Northern | Switzerland | 1960 | 1 | 32.4 |
| Northern | England | 1959 | 1 | 41.7 |
| Northern | Germany | old | 5 | 28.4–39.1 (mean 31.8) |

*Résumé.* L'acide cannabidiolique pouvant être considérée comme la substance initiale dans la conversion graduelle des composants de la résine du chanvre (*Cannabis sativa*), le taux de la fraction acide peut servir d'indication sur l'avance du processus de «mûrissement» de la résine. La teneur en acide a été trouvé la moins élevée dans la résine du chanvre provenant de régions tropicales, ce qui s'explique par la conversion plus avancée dans des variétés dévelopées sous un climat favorable et chaud. D'après les résultats obtenus, cette conversion semble continuer pendant la conservation de la drogue.

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[11] We are indebted to the Division of Narcotic Drugs of United Nations for having kindly supplied most of cannabis samples examined in this study.

## Cerebral Vascular Action of Bradykinin in the Dog

One of the most important biological effects of bradykinin is its action on the vascular system[1]; moreover the demonstration of the presence of kinin-forming enzymes in perfusates of different systems[2] supports the view that bradykinin may play a role in the regulation of local blood flow in various vascular districts[3]. The presence of these enzymes also in the perfusates of the ventricular system of the cat[4] suggests the need for a critical evaluation of the effects of bradykinin on cerebral vascular flow. Moreover, since the description of its chemical composition and its synthesis[5], investigations of its effects can be carried out with much greater reliability.

In the present study, the vascular reactions of the brain vessels were studied in the chloralosed dog by means of a previously developed technique consisting of the registration of the intracranial venous pressure by means of a catheter introduced in a craniad direction into the peripheral portion of the external jugular vein[6]; simultaneous tracings of arterial pressure, intracranial venous pressure, other vascular phenomena (systemic venous pressure, nasal plethysmogram[6] venous outflow from the superior sagittal sinus[7]) and respiration were registered on a 6-channel Grass Polygraph. The effects of intravenous administration

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