then normalized by day 35. In contrast to these results, at the higher dose the colony formation resembles the data obtained after the single dose of 400 mg/kg B1. The maximum was found on day 3. From day 6 the values are comparable to the control. In these in-vivo experiments, there is no recognizable dependence of dilution of MP.

This is to our knowledge the first time that a CFUc stimulating effect by a cytostatic drug has been observed. All previous publications employing cytostatics in vivo or in vitro in this agar culture system showed a decrease in the number of leucopoietic stem cells[9]. This finding is in particular described for nitrogen mustard and the hydrazine derivative procarbazin[10]. In some cases the decrease is followed by a later rebound increase. The effect of B1 seems to depend on a direct action on the CFUc or its precursor(s), as the increase in colonies not only occurred during the treatment of the animal, but also when the bone marrow was incubated with this substance in vitro. The occurrence of the synergism between B1 and CSA, as shown in the in vitro experiments, may be explained by a greater sensitivity of CFUc to CSA under the influence of B1.

In Ehrlich ascites tumor cells (EAT), we could show that B1 is not able to penetrate the cell but affects the cell membrane. However, a penetration is probable when dimethylsulfoxid (DMSO 0.5% v/v) is present in the culture medium. Under this condition, the glycolysis of tumor cells was reduced vigorously by B1 in contrast to a strong stimulation in absence of DMSO[12]. Therefore we investigated in an additional experiment the influence on CFUc after preincubation with B1 for 5 and 30 min in the presence of DMSO (0,5% v/v) in the agar culture. As shown in table 3, the colony-forming capacity decreased strongly in contrast to the control when DMSO was present. Prolongation of the incubation time and lower concentrations of MP enhanced the inhibition.

As an indication of the membrane alteration caused by B1, we found an increase in SH-groups at the cell surface. The increase was 180% as compared with the control. This similar alterations at the surface of CFUc might be responsible for the higher sensitivity to CSA.

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Reconsideration of a test for dopaminergic stimulation: Inability of apomorphine to induce mouse jumping

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Summary. Apomorphine was administered parenterally to mice in an unsuccessful attempt to induce amphetamine and L-3,4-dihydroxyphenylalanine-like elicited jumping. The efficacy of jumping behavior as an indicator of dopaminergic overstimulation is criticized in light of the results.

In recent years, many experimental models have been proposed for the study of dopamine systems in the brain[1,2] in an effort to elucidate the role they may play in such disorders as Parkinson's disease and schizophrenia. Several articles[3-5] have attributed amphetamine and L-3,4-dihydroxyphenylalanine (L-DOPA) induced mouse jumping to dopaminergic overstimulation similar to that yielding stereotypic behavior in rodents treated with amphetamine, apomorphine, or other drugs. If dopaminergic overstimulation were in fact responsible for the observed behavior then dopaminergic antagonists should effectively attenuate the effect. Lal et al.[5] showed dose-dependent antagonism of the jumping with neuroleptics, but not with other psychoactive agents, including apomorphine. It is reasonable that apomorphine, a dopamine like agonist[6], should induce or even potentiate behavior believed due to dopaminergic stimulation when administered subsequent to amphetamine and L-DOPA. In view of this anomaly, attempts were made to elicit mouse jumping with various doses of apomorphine and under the conditions reported[5].

Methods. Random bred, male Swiss Webster albino mice (Laboratory Supply Co.) were housed in air conditioned quarters with no light from 11.00–23.00 h, and were allowed food and water ad libitum. All animals weighed between 24–31 g. They were treated with i.p. apomorphine HCl dissolved in 0.9% saline. The mice were immediately placed in separate glass jars (15 × 24 cm) for observation. Control animals, as well as those treated with 5 mg/kg apomorphine or less were observed for 30 min. Mice treated with larger doses were observed for 1 h. As in previous reports, a jump response was defined as simultaneous lifting of all paws from the floor.

Results. Control animals averaged 1 jump during the observation period (table). Confirming earlier results[5], 64% of the controls did not jump, while 36% jumped 1–10 times. The mouse jumping caused specifically by combined amphetamine and L-DOPA treatment was not induced with apomorphine over a wide range of doses (table). If jumping were due to dopaminergic overstimulation, it is difficult to explain why apomorphine, an acknowledged direct dopaminergic agonist, failed to stimulate this behavior. It should be noted that stereotypy, a well recognized and much studied attribute of dopaminergic overstimulation[2], was seen with all but the lowest dose of apomorphine. While the duration and intensity of the stereotypic behaviors (gnawing, licking and sniffing) appeared to be dose dependent, experimental conditions did not lend themselves to accurate quantitation.

Discussion. The discrepancy between the present report and the results presented and conclusions drawn in previous papers[3-5] may be attributable to several factors. In contrast to the site specificity of apomorphine action, amphetamine

Frequency of mouse jumping elicited by apomorphine

Drug	Dose (mg/kg)*	Mean mouse jumps**
Saline		1 (25)
Apomorphine	0.4	0 (8)
	1.0	0 (8)
	5.0	0 (8)
	7.5	0 (8)
	10.0	0 (8)
	25.0	0 (6)
	50.0	0 (4)

* Observation period was dose-dependent. See methods. ** Parenthesized numbers indicate mouse population size.

has been postulated[6] to have both direct and indirect agonist actions on both dopamine (DA) and norepinephrine (NE) activated neurons. Exogenous L-DOPA is not only converted to catecholamines in DA and NE neurons[6], but it is also taken up by serotonin neurons[7] and exerts an influence on various behaviors due to increased functional activity at serotonin synapses[8]. The importance of noradrenergic systems in jumping behavior has not been eliminated since the NE blocker tested, phentolamine, passes only poorly into the brain and causes few of the biochemical and functional changes seen with centrally active adrenergic blocking agents[9]. A further difficulty with the jumping behavior model is the inability of either amphetamine or L-DOPA alone to induce jumping[4].

The inhibition of L-DOPA and amphetamine induced jumping by neuroleptics and the reversal of this inhibition by anticholinergic agents has been cited[3] as evidence for the specific mediation of jumping behavior by DA systems. Many behavioral effects of neuroleptics are reversed in this manner[3], but the only area where biochemical antagonism has been well established is the Corpus Striatum[10]. If striatal DA systems were mediating jumping behavior, apomorphine, a potent DA agonist at this site, should also elicit jumping. It is possible that the inhibition of jumping by neuroleptics is a nonspecific antagonism secondary to the induction of catalepsy, which effect is elicited with relatively low doses of potent neuroleptics[11,12] and reversed by anticholinergic drugs[12,13].

In light of the multiple sites for activity and actions of the agonist drugs used in previous reports, and particularly in consideration of the results presented here, the proposal that jumping behavior induced by L-DOPA and amphetamine is specifically due to dopaminergic stimulation must be questioned. Finally, drugs such as narcotic antagonists, 5(1,3-dimethylbutyl)-5-ethylbarbituric acid, naphthyloxyacetic acid and theophylline have all been reported to induce mouse jumping[4], making a precise mechanism for jumping behavior very difficult to determine. Thus, with the availability of well established and pharmacologically specific models for dopaminergic stimulation[1,2], the value of employing jumping behavior for this purpose is limited.

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Retrograde lymphatic spread of colonic carcinoma to the liver

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Summary. Retrograde lymphatic permeation of the liver by a malignant neoplasm is an unusual phenomenon and has apparently not been reported with colonic carcinoma. This paper presents such a case; the features of the lesion are similar to those described for other primary sites.

Nonmetastatic invasion of the liver via lymphatic vessels is unusual[2-4]. Retrograde lymphatic permeation has been reported most frequently with gastric carcinoma; it also occurs with carcinoma of the pancreas, ovary, and cervix uteri[2,4]. Tumour deposits occur typically in the region of the porta hepatis and its lymph nodes, with extensions into the liver along the major portal tracts[5]. 'In this way, there may be formed a branching frond-like tumour mass, most bulky at the porta and becoming gradually attenuated peripherally, its ramifications corresponding to those of the portal tracts which the tumour thus delineates in grotesque fashion'[4]. Retrograde lymphatic spread does not seem to have been reported for colonic carcinoma, and has not been observed by R.A. Willis (personal communication).

Clinical summary. A 63-year-old man underwent right-sided hemicolectomy for a moderately differentiated adenocarcinoma of the caecum. 3 months later, multiple metastatic nodules were found in the abdominal wall and mesentery. He died 1 month later.

Autopsy findings. Cardiovascular system: thrombosis of the right external iliac, femoral, popliteal and deep calf veins. Respiratory system: bullous emphysema. Embolism of the left apical branch of the pulmonary artery. Infarction of the left apical segment, with infection and abscess formation. Alimentary system: faecal peritonitis. The site of leakage could not be identified. There was evidence of a previous Billroth II gastrectomy. The small intestine was distended and congested; numerous fibrinous adhesions were present. The carcinoma had recurred at the site of previous anastomosis. However, the anastomotic region was not fixed to adjacent structures and there was no evidence of contiguous spread of the tumour.