had more voluminous diarrhœa. Thus the low stomach acid of Bengali cholera patients (treated the same way as the volunteers[6]), and its gradual improvement during several months after convalescence,[6] must represent idiopathic hypochlorhydria which predisposes to cholera and happens to improve afterwards. Based on the percentage of patients with hypochlorhydria and the cholera and N.V.C. case-attack rates in Bangladesh,[15 17] the estimated minimum prevalence of Bangalees with hypochlorhydria is as high as 1–2 per thousand persons.

Normal infants reportedly produce less stomach acid than adults,[18] and infant hypochlorhydria is linked with malnutrition.[19] The specific causes remain unknown, but may include deficient dietary protein or vitamin-B intake.[20] Nutritional deficits during the 1971 war and the 1974 famine in Bangladesh may have increased hypochlorhydria and could account for different results in this and previous studies,[6 9] and for the increase in cholera noted during 1971–5 at the C.R.L., Dacca.

The susceptibility of hypochlorhydric persons to cholera is presumably due to increased survival of ingested vibrios during stomach transit. Basal or postprandial acid secretion are roughly the conditions ingested pathogens must survive if they are to colonise the gut, and are more physiological and convenient indicators of susceptibility than peak betazole-stimulated secretion. They also correlate better with vibrio survival and diarrhœa severity. While volunteers received bicarbonate with the pathogenic bacteria, their capacity rapidly to neutralise it and reacidify the gastric contents is known to vary;[3] those with low acid production would presumably be unable to acidify the ingested bicarbonate rapidly, with resultant greater vibrio survival. Severity of diarrhœa is related to vibrio dose.[3]

The amounts of surface water normally consumed in endemic areas contain few vibrios, yet more than 10^{11} vibrios are needed to induce cholera in normochlorhydric volunteers,[3] and gastric aspirates with pH<2·4 can kill even 10^{10} vibrios/ml in 1–5 min. Hypochlorhydria therefore seems to be vital for natural cholera transmission, and screening to detect hypochlorhydria might be useful as a public-health measure aimed at identifying and vaccinating or otherwise protecting susceptible individuals. This might make vaccination[21] and drinking-water improvement programmes[22] more effective in reducing cholera or allied diarrhœas.

Identification of specific causes of hypochlorhydria could lead to dietary or other prophylaxis aimed at normalising acid secretion, thereby reducing gastrointestinal bacterial colonisation.[23] Such colonisation is common in the tropics, and has been linked with gastritis[19] and malabsorption[24] in addition to diarrhœa.

Environmental fæcalisation alone may not be sufficient to maintain high diarrhœa case-attacks. In developing countries, hypochlorhydria may be a key link between malnutrition and enteric disease prevalence.

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CANNABIS, HYPOCHLORHYDRIA, AND CHOLERA

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Summary In 90 volunteers participating in a vaccine-development programme consumption of beer more than 3 days a week was linked with high stomach acid output, and smoking of cannabis >2 days a week was linked with low acid output. In 92 volunteers challenged with *Vibrio cholerae* or enterotoxigenic *Escherichia coli*, heavy use of cannabis was associated with more voluminous diarrhœa. Cannabis use may be an important factor predisposing to severe diarrhœa.

Introduction

A STUDY of stomach acid production before and after induced cholera in U.S. volunteers revealed that cholera did not reduce stomach acid secretion, but that the

TABLE I—SUMMARY OF GROUPS STUDIED

Pathogen (dose and no. of subjects)	Basal and peak acid tests		No. with diarrhœa
	Admission	10 days later	
V. choleræ, classical biotype. Inaba 569B (10^6, 12)	11	11	10
Ogawa 395 (10^5, 6; 10^6, 15)	20	20	16
El Tor biotype. Inaba N16191 (10^5, 5; 10^6, 10)	5	5	7
Inaba P27459 (10^5, 5; 10^6, 11)	5	5	10
Ogawa N15870 (10^5, 5)	–	–	2
Ogawa N16117 (10^5, 4)	4	4	0
E. coli 2528C1 (10^8, 19)	–	–	12
None (45)	45	–	–
Total 137	90	45	57

diarrhœa which developed after ingestion of *Vibrio choleræ* was more severe in volunteers with low stomach acid.[1] The finding of low acid production among apparently healthy young American adults (group I, table I) led to ætiological investigations in subsequent groups.

Volunteers and Methods

Methods of volunteer selection, orogastric intubation for aspiration of stomach secretions, and basal (1 h) and betazole (ametazole) hydrochloride ('Histalog')-stimulated stomach acid measurements are described elsewhere.[1 3–5] 137 volunteers (104 males, 33 females; 23±0·5 yr; 70·5±1·4 kg) were studied. Initial examinations included psychological evaluation. Basal and peak (post-histalog) acid production of 90 individuals were measured 1–3 days after admission to the quarantined study ward, and this investigation was repeated 9 days later in 45 subjects. Volunteers were interviewed by at least two interviewers on two or more occasions concerning food, alcohol, and drug usage, and gave identical responses in 94% of cases. Total consumption of beer, the commonest alcoholic beverage used, correlated closely with total alcohol intake, so beer use was quantitated as days beer was taken per week and cans of beer used per day. Reported use of cannabis ("pot", "grass", or marijuana, smoked in cigarettes called "joints" or "reefers") was quantitated as days cannabis was used per week and joints used per day. Reported preadmission alcohol and cannabis use were correlated with stomach acid measurements. Alcohol and cannabis use were prohibited on the study ward.

92 of the volunteers participated in vaccine development studies and ingested bacterial pathogens (*Vibrio choleræ* or *Escherichia coli* strain E2528C1, which produces thermolabile enterotoxin[3]) with 150 ml water and 2 g $NaHCO_3$ after a 2 h fast. Diarrhœa was defined as at least three grade-III liquid stools (stools which take the form of the container[4]) within 24 h. Diarrhœa severity, indicated by measured total diarrhœa volume, was correlated with alcohol and cannabis use. Treatment included standard oral and intravenous rehydration solutions and antibiotics (tetracycline in cholera studies, neomycin in *E. coli* studies). Volunteers received regular diets. Table I summarises the study groups.

Results

Beer and Stomach Acid

On the basis of initial test results, volunteers could be divided into high, normal and low acid-producers. High peak acid production (peak>16 mmol HCl/h), but not high basal acid production, correlated with high beer intake (more than 3 days a week). Beer intake of heavy cannabis users exceeded that of light users (2·9±0·7 *vs* 1·4±0·1 days a week). All figures are means ±S.E.M.

Cannabis and Stomach Acid

Reported past prevalence of cannabis use was 74%, and current prevalence (1 or more days a week) was 52%. Of all those individuals, beer drinkers included, who smoked cannabis more than 2 days a week ("heavy users"), 44% had no free basal acid (pH>3·0), compared with 21% of those using cannabis less often (P=0·028, Fisher's test). Heavy beer drinkers excluded, 67% of those smoking pot more than 2 days a week lacked free basal acid (fig. 2). Initial histalog-stimulated peak acid production was lower in heavy cannabis users than in light users or non-users (P<0·02, two-tailed *t* test; fig. 3), but tests repeated after 9 days on the ward showed rises in peak acid production which were most striking in heavy cannabis users during the period of induced cholera (+9·0±2·4 mmol HCl/h; P<0·02, n=12). A smaller, borderline significant rise occurred in light users (0·1>P>0·05, n=17) and no significant rise was seen in non-users (n=16).

The change in peak acid between tests did not correlate with beer intake; however, among persons reporting cannabis use >2 days a week, those also drinking beer

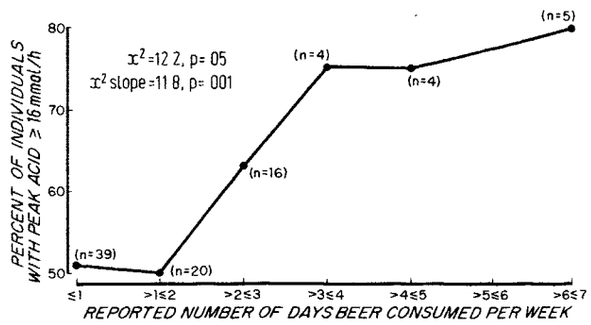

Fig. 1—Relation of beer-drinking to peak acid secretion.

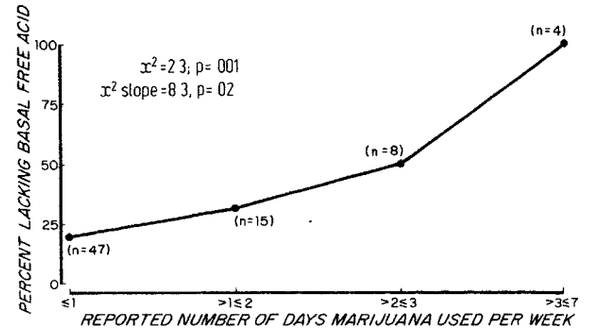

Fig. 2—Relation of marijuana use to absence of basal free acid (heavy beer drinkers excluded).

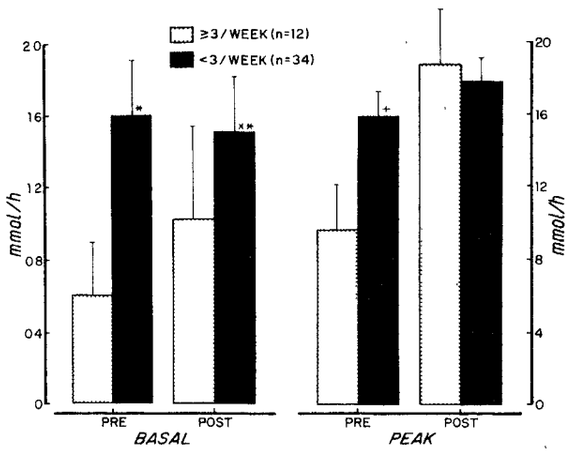

Fig. 3—Relation of cannabis use to acid secretion before and after diarrhœa.

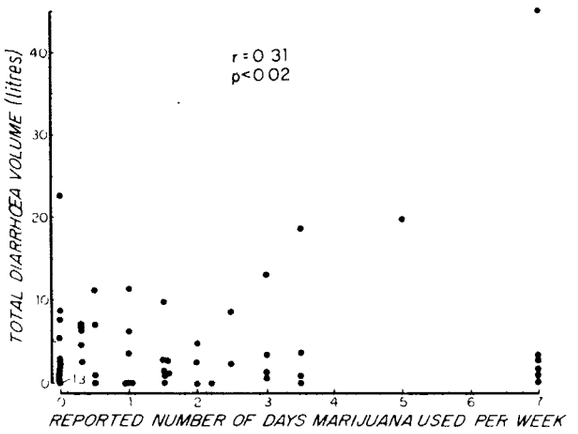

Fig. 4—Relation of cholera diarrhœa volume to marijuana use. The 5 subjects on lower-right were all heavy beer drinkers.

more than 3 days a week tended to have normal or high peak acid on initial tests, suggesting that high alcohol intake may overcome the depression of acid production associated with cannabis (table II). After exclusion of subjects drinking beer 3 or more days a week, the relation of cannabis use to basal or peak acid production was significant (r=−0·29, P<0·02 for both). Heavy and light cannabis users did not differ regarding volume of basal (61±6 ml), peak (48±3 ml), or total (253±16 ml) gastric aspirates; in volume change between serial tests (Δ=−14±7, +6±4, and −17±20, respectively); nor in length of tube swallowed (23±1 inches in both groups; Δ=−0·4±0·7 inches between tests). Review of individual psychological evaluations revealed no cluster of personality traits characteristic of users or non-users of cannabis of beer which related to acid secretory status or the rise in peak acid production seen between tests.

Cannabis and Diarrhœa

Cholera case-attack rate was 88% among heavy users (n=17) and 37% among light users (n=56; P=0·02). Volume of cholera (fig. 4) and *E. coli* diarrhœa correlated significantly (both P<0·02) with cannabis use but not with beer intake. Cannabis (not beer) usage correlated with diarrhœa duration (P=0·05), but neither beer nor cannabis usage correlated with incubation. Since heavy cannabis users had more diarrhœa and the correlation coefficients of the Δ peak acid between tests *vs* diarrhœa volume or cannabis use were equal (r=0·39, n=45, P<0·02), the relative importance of factors influencing the peak acid response (lack of cannabis during study, cholera itself, stress, or hospital diet) could not be determined.

TABLE II—ACID OUTPUT, COMPARED IN HEAVY CANNABIS USERS WITH DIFFERENT INTAKES OF BEER

	No. of persons			
	Basal free acid		Peak acid	
Beer consumption	0	+	<16 mmol/h	≥16 mmol/h
≤3 days/wk	8	6	10	6
>3<7 days/wk	2	8	1	7
–	P=0·07		P=0·03	

Discussion

The low acid secretion of cannabis users could be due to central-nervous-system or local gut effects. Psychological profiles revealed no obvious "cannabis personality" relatable to hypoacidity. The volume of gastric secretions aspirated was similar in cannabis users and non-users, so the cannabis link with low acid seems unrelated to any effect on gastric emptying. Tetrahydrocannabinol increases cell adenylcyclase activity,[5] which has been linked in some studies to low acid production[6] and to the genesis of cholera and *E. coli* diarrhœas.[7] Cannabis might act both by reducing stomach H^+ secretion and by enhancing the effect of enterotoxins on intestinal-cyclase activity, leading to greater survival of ingested pathogens during stomach transit, and greater diarrhœa volume after intraintestinal production of enterotoxins.

Cannabis indica is widely used in the Indian subcontinent and in other developing areas where drinking water and food often harbour intestinal pathogens. This may account for some of the hypochlorhydria seen there in adults[1 5 8 9] and suggests a possible link with the high incidence of severe diarrhœas in such areas. Tourists from developed nations who travel abroad and indulge in "pot" or "ganja" while imbibing local pathogens may also be at high risk of contracting severe *turista*, unless protected by their alcohol intake. Lastly, could there be a connection between increased cannabis use in the West since 1967 and the sharp decline in peptic-ulcer incidence during that period?[10]

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CONTROLLED STUDY OF HYPERTRANSFUSION DURING REMISSION INDUCTION IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKÆMIA

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Summary In a prospective, controlled trial 26 anæmic, neutropenic children with newly diagnosed acute lymphocytic leukæmia were randomised in pairs to receive either transfusion to a hæmoglobin of 10–12 g/dl where clinically indicated (group A) or hypertransfusion to a hæmoglobin of 16–18 g/dl (group B). Compared with group A (11 of 13 transfused), group B (all transfused) had a significantly more rapid rise in neutrophils at 7 and 10 days post-transfusion, a lower incidence of infection, and less interruption to chemotherapy. Hypertransfusion restored the myeloid/erythroid ratio to normal in bone-marrow of 5 of 6 children and the proportion of early myeloid precursors was greater than in controls.

Introduction

NEUTROPENIA often complicates the treatment of malignant disease, predisposing the patient to infections and interrupting chemotherapy. Animal studies have provided evidence that the erythroid and granulocytic pathways may compete for progenitors arising from pluripotential hæmopoietic stem cells (stem-cell competition) and that, under certain circumstances, granulopoietic activity can be enhanced after red cells have been hypertransfused to reduce the demand for erythroid progenitors.[1-8] Since normal bone-marrow cells are reduced in untreated childhood acute lymphocytic leukæmia (A.L.L.), it is possible that in untreated A.L.L. the production of granulocyte precursors is compromised by competing demands for the production of erythroid precursors.

A preliminary study in children undergoing cytotoxic treatment for malignant disease demonstrated a more rapid recovery from neutropenia, less interruption to chemotherapy, and fewer infections in the hypertransfused group than in controls.[9] The children studied were a heterogeneous group with different neoplasms and modalities of treatment, thus raising the possibility that the beneficial effects observed were not directly attributable to hypertransfusion. We now report the results of a prospective, randomised, controlled study of hypertransfusion in neutropenic, anæmic children with previously untreated A.L.L.

Patients and Methods

Children with newly diagnosed A.L.L. and a total white-cell count $<30\times10^9$/l were randomised into the study if they had a hæmoglobin of <10 g/dl and a polymorph neutrophil (P.M.N.) count of less than $0{\cdot}5\times10^9$/l. 26 children (18 boys and 8 girls aged 18 months to 14 years and 2 months, median 4 years) were randomised in pairs to groups A and B. Children randomised into group A received transfusion only when it was clinically indicated (11 of 13 transfused). The decision to transfuse was made by a clinician not involved in the study. The transfusion was given in the form of packed red cells to a hæmoglobin of 10–12 g/dl. Children randomised into group B were all transfused to a hæmoglobin of 16–18 g/dl immediately after randomisation. In all children, hæmoglobin, platelet-count, and total white-cell and differential counts were estimated three times a week for 14 days and subsequently twice weekly for a further 14 days. Standard automated techniques (a model FN Coulter counter and a Technicon 'Autocounter') were used. Differential counts were done on 100 white blood-cells by hæmatology laboratory staff not involved in the study and unaware of the patient's randomisation. Temperature was monitored 4-hourly in all patients and febrile episodes exceeding 38·5°C were investigated by routine cultures and, where applicable, chest X-rays. Infections during the first 4 weeks of treatment were counted and categorised as: fevers without proven infection, which include fevers of unknown ætiology or those possibly related to malignancy and/or chemotherapy; minor infections including gastroenteritis, pharyngitis, and otitis media; or major infections such as septicæmia and pneumonia.[10]

All children were treated with appropriate antibiotics for a diagnosed infection or with a combination of gentamicin and cephaloridine for pyrexia of unknown origin. Platelet transfusions were given only when considered to be necessary for control of clinical bleeding episodes (which did not differ in frequency between the groups). Anti-leukæmic chemotherapy was identical in all children and consisted of vincristine (2 mg/m²/week) and prednisolone (50 mg/m²/day) according to our leukæmia study protocol. Interruptions to chemotherapy were noted during the first 4 weeks of treatment. Treatment was deferred by clinicians not involved in the study and only when drug toxicity was considered to be present. Bone-marrow aspirations were done on day 14 in the last six pairs (pairs 8–13). Where possible, 200-cell differential and myeloid/erythroid ratios were determined in films stained with Leishman stain as well as in films stained with a hæmoglobin-specific stain,[11] to ensure accurate differentiation of erythroid precursors from other mononuclear cells in the bone-marrow.

Serum was collected on day 14 for estimation of erythropoietin in five pairs. A modification of a previously described in-vitro bioassay was employed with a lower limit of sensitivity of 0·05 units per ml of serum[12] in an attempt to identify children with elevated erythropoietin levels.

The study was approved by the hospital ethics subcommittee beforehand. Statistical analysis was done with the non-parametric Wilcoxon rank-sum test and the χ^2 test with Yates' correction.

Results

Hæmoglobin values, absolute P.M.N. counts, and the incidence of infections and interruptions to chemo-

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