the fertility rate is not known. In view of our observations, perhaps other physicians could investigate the hormonal status of galactosæmic women in their care.

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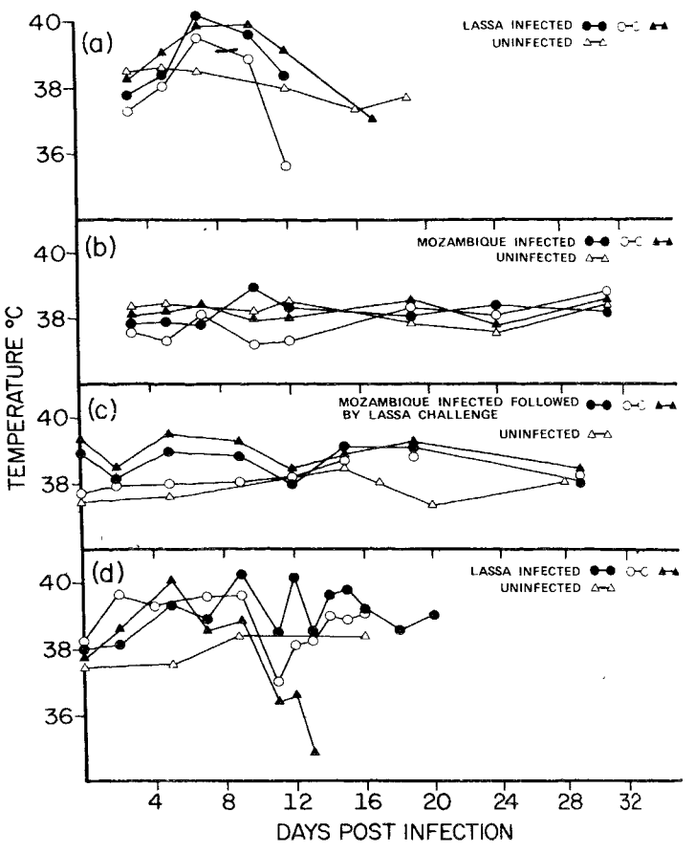
PROTECTION OF RHESUS MONKEYS FROM LASSA VIRUS BY IMMUNISATION WITH CLOSELY RELATED ARENAVIRUS

SIR,—Lassa fever virus has been reported to produce, in the rhesus monkey, a disease clinically similar to the severe form observed in man.[1] Using this animal model, we have prevented clinical Lassa disease by prior infection with an apparently benign arenavirus, Mozambique virus, originally isolated from the rodent *Mastomys natalensis* in South-east Africa. Immunologically Mozambique virus is closely related to Lassa virus, as strong cross-reactions by both complement fixation and indirect immunofluorescent serological methods indicate.

Two groups of three monkeys weighing 3·6–4·1 kg were inoculated subcutaneously with 10^4 median tissue-culture infecting doses ($TCID_{50}$) and $10^{3.5}$ $TCID_{50}$ of Lassa (Josiah strain) or Mozambique viruses, respectively. The animals were placed in individual cages, and each group was housed in a separate HEPA-filtered enclosure within our maximum containment laboratory. A non-infected monkey was housed with each group as an uninoculated control. In the three animals inoculated with Lassa virus fever developed within 7 days (see figure, a). These animals also had conjunctivitis and anorexia and became progressively lethargic. Two of these animals died on the 12th day post-inoculation, after their temperatures had declined to subnormal values; on day 17, the third animal, which was moribund, was killed and sent for necropsy. In contrast, the Mozambique-inoculated monkeys had a lower fever or none (figure, b) and no clinical signs. All three of the animals given Lassa virus had a viræmia for at least 5 days beginning on the 7th day after inoculation. No virus was recovered from the Mozambique-inoculated monkeys at any time. On day 28, indirect immunofluorescent antibody titres to Lassa virus in both the Lassa-infected and Mozambique-infected animals were 1:256 to 1:512. The two control animals never showed signs of illness and antibodies to either virus did not develop over a period of 120 days.

75 days after primary infection, the Mozambique monkeys were each challenged with $10^{3.5}$ $TCID_{50}$ of Lassa virus inoculated subcutaneously. Three Lassa control monkeys weighing 5·0–5·9 kg were similarly inoculated with Lassa virus. One uninoculated control monkey was again placed with each infected group. None of the first group displayed fever, viræmia, or clinical signs, but the three Lassa control monkeys all became ill, with fever, and had virus in their blood (figure, c and d). One of them died after 13 days, and another, in poor condition, was killed on day 16; the third survived infection. In the Mozambique-infected group of monkeys immunofluorescent antibodies to Lassa virus had risen fourfold to eightfold by 12 days after the Lassa virus challenge.

Although virological, pathological, and immunological studies of these animals are still incomplete, our data confirm that the rhesus monkey is useful as a model for human Lassa virus infection. Our data also suggest the possibility that the Mozambique virus could be used for preparation of a live or inactivated vaccine against Lassa fever in man. We are attempting to determine whether Mozambique infection produces antibodies against surface antigens of Lassa virions and whether the two viruses show significant chemical differences. Further information on the pathogenicity of the Mozambique agent for humans in Southern Africa is also needed.



Fever in four groups of rhesus monkeys.

(a) Lassa virus only; (b) Mozambique virus only; (c) Mozambique virus followed by Lassa challenge; (d) Lassa infected.

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VASOPRESSIN ANALOGUE IN METHADONE DETOXIFICATION OF HEROIN ADDICTS

SIR,—The vasopressin analogue, des-glycinamide[9]-arginine[8]-vasopressin (DGAVP), which is practically devoid of the peripheral endocrine action of the parent hormone,[1] decreases heroin self-administration in rats.[2,3] This was interpreted as indicating an attenuating action of DGAVP on the reinforcing effects of heroin. We have investigated DGAVP clinically in heroin addicts on methadone detoxification. In the detoxification programme methadone, 20 or 40 mg daily by mouth, is given to outpatients. Urine is collected daily and tested for the presence of drugs. The daily methadone dose is decreased gradually, starting 2–3 weeks after the beginning of therapy—but not if morphine is found repeatedly in the urine, indicating that heroin is still being taken despite methadone treatment. Treatment is assessed from the time course of at-

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tendance at the clinic and from the number of morphine-free urine samples.

Twelve patients with moderate heroin addiction who had asked for detoxification volunteered to take part in a study in which, during the first 5 days of methadone therapy, the addicts were given a sublingual tablet containing 1 mg DGAVP (Organon International) or placebo, once daily. Allocation was double-blind. The patients were examined daily for 3 weeks. Special questionnaires were completed by patient and doctor. Urine was analysed, and the patient's blood-pressure, pupil diameter, and so on were checked.

Six patients received DGAVP and six placebo. The mean ages (±SEM) were 22±2 and 23±2, respectively. The history of the patients, their present circumstances, addictive behaviour, the amount of drug being taken, and the drug content of the urine just before the start of the study were comparable in the two groups.

One patient in each group did not complete the study for personal reasons most probably not related to the addictive behaviour. The remaining five patients in the DGAVP group continued with the programme and had their daily methadone dose lowered after 2–3 weeks. In contrast, three of the five patients receiving placebo continued their addictive behaviour as could be inferred from the presence of morphine in the urine and non-attendance at the clinic after 7–10 days. The remaining two patients on placebo needed an increase in their methadone dose on days 3 and 11. During the 5-day period the median percentage of urine samples with detectable morphine and/or cocaine per individual was 10% in the six DGAVP addicts and 100% in the six controls. A similar difference was found in the 5-day period after cessation of the DGAVP and placebo treatment. The medical attendant judged the methadone detoxification of the patients receiving DGAVP to have been more successful than that of the patients on placebo. No side-effects were observed with DGAVP treatment. During the 5 days of treatment the blood-pressure decreased in the patients receiving placebo but not in those receiving DGAVP.

These preliminary findings suggest that DGAVP facilitated the methadone detoxification of heroin addicts, and that this approach warrants further investigation.

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ARE SERUM-COPPER LEVELS IMPORTANT IN BLEOMYCIN THERAPY?

SIR,—Lin et al.[1] have advocated the use of diethyldithiocarbamate as a copper chelator to enhance the efficacy of the antineoplastic agent, bleomycin. They suggest that diethyldithiocarbamate might be a more effective copper chelator for this purpose than penicillamine.[2] We would like to point out that data from two independent sources remove the original rationale for lowering copper levels when treating with bleomycin.[3,4] As Lin et al. acknowledge, this rationale was based on the results of biochemical studies on the attack of isolated DNA by bleomycin: DNA degradation in the presence of sulphydryl compounds was inhibited by Cu^{2+}. These data led Preece et al.[2] to suggest that the clinical efficacy of bleomycin could be improved by the lowering of serum-copper levels with agents such as penicillamine. However, in later experiments we found that preformed copper-bleomycin complexes and metal-free bleomycin had similar cytotoxic and DNA-damaging effects on intact cultured mammalian cells. Our results were supported by those of Takahashi et al., who also reported that treatment with copper-bleomycin results in incision of DNA in vivo. They showed that in vivo copper is removed from the copper-bleomycin complex, leaving the bleomycin free to attack DNA. The removal of copper was shown to involve intracellular reduction of the cupric ion and transfer of the copper to cellular proteins.

Preece et al.[2] reported that the administration of penicillamine before bleomycin treatment enhanced the cytotoxic effect of bleomycin, as measured by marrow suppression and found that the administration of penicillamine before treatment of patients with bleomycin, either alone or as part of a combination of oncolytic drugs, produced an encouraging response. Since it now appears that copper does not affect the toxicity of bleomycin towards whole cells an alternative explanation must be sought. One possibility is that the lowering of serum-copper levels may alter the subsequent distribution and excretion of bleomycin, as the copper chelate of bleomycin may be substantially different from metal-free bleomycin in these respects.[5] Alternatively the penicillamine treatment may also affect the distribution of other, perhaps more critical metals, such as cobalt, zinc, and iron. Serum-zinc levels decrease after bleomycin administration.[6]

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DIETARY SOURCE OF ω-3- EICOSAPENTAENOIC ACID

SIR,—Dr Dyerberg and Dr Bang (Sept. 1, p. 433) suggest that partial dietary substitution of ω-6 arachidonic acid by ω-3-eicosapentaenoic acid (EPA) might reduce the incidence of thrombotic disorders, including myocardial infarction. How could this substitution be done in practice? The Eskimo diet —involving consumption of large amounts of the meat of whales, seals, seabirds, and fish is an unrealistic option.

The 1977 National Food Survey shows that the average person in the U.K. consumes 130–140 g/day of fat, mainly from dairy products, meat products, margarine, lard, and frying oils and fats; only 1% derives from fish. Such a diet would supply, in g/day, saturated fat 61, monounsaturated fat 51, linoleic acid 20, linolenic acid 3·3, and eicosapentænoic acid 0·1. Thus the preponderance of arachidonic acid as opposed to EPA found in blood lipids presumably reflects the high proportion of precursor linoleic acid in the diet compared with the levels of linolenic acid (the precursor of EPA) or EPA itself. To alter this balance dietary linoleic acid should be decreased (without decreasing the linolenic acid) or the linolenic acid level increased (without increasing the linoleic acid). Since linolenic acid and linoleic acid usually go together the diet manipulation would be difficult.

Increased consumption of oily fish such as mackerel or sardines would substantially increase the intake of preformed EPA. Unfortunately, in the U.K. oily fish are much less popular than white fish.

A realistic way of improving the EPA level of the diet is the regular consumption of an EPA rich oil from fish, such as cod-liver oil. Two teaspoons daily (10 g) would contribute 1 g of EPA to the diet, about ten times the present level of intake. To

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