as this is the time required to pump the suspension from the culture vessel to the calorimetric chamber.

However, sulphadimidine (which was only used with *E. coli* 1) had no effect on heat output at the MIC level and even at a concentration of 30× MIC had only a slight and transitory effect. This may reflect the relatively high bacterial concentration used in the calorimetric experiments (2×10^7 cells ml^{-1}) compared to that used in the tube dilution method for determining MIC's (2×10^5 cells ml^{-1}). (This apparently large difference in the bacterial cell concentrations, however, had no effect on the response to MIC's of the other antibiotics.) The dependence of sulphadimidine MIC determinations on inoculum density has been reported[13]. It is possible that if a calorimeter able to monitor heat outputs from a population as small as 10^5 cells ml^{-1} were available, a better correlation could be obtained. It is also well-established[13] that some bacterial culture media contain sulphadimidine inhibitors (p-amino benzoic acids) which interfere with the determination of sensitivity to sulphadimidine, using standard disc diffusion techniques. This problem is usually overcome by the incorporation of lysed blood into such media. It is possible that the medium used in the work reported here contained such inhibitors.

The results, therefore, indicate there are measurable changes in heat output by metabolizing bacteria when exposed to concentrations of most antibiotics equivalent to the MIC as determined by the tube dilution method. Moreover, these changes occur within 8 min or less after exposure of the culture to the antibiotic and therefore suggest that this technique could be adapted for the rapid assessment of sensitivity of bacterial isolates to particular antibiotics in the diagnostic microbiology laboratory.

Furthermore, the flow microcalorimeter is easily automated, and, if a multi-channel device were available, a large volume handling system could be devised with a rapid through-put potential.

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15 Medium constituents (g l^{-1}): glucose, 1; K_2HPO_4, 4.2; NaH_2PO, 3.9; peptone 1; yeast extract, 0.2; $MgCl_2$, 0.13; $CaCO_3$, 0.0003; $FeSO_4\cdot7H_2O$, 0.007; $MnCl_2\cdot4H_2O$, 0.001.

Anticonvulsant action of YG 19-256 in baboons with photosensitive epilepsy

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Summary. YG 19-256, 4-(1,3,4,9b-tetrahydro-5 methyl-2H-indeno[1,2-c]pyridine-2-yl)-2-butanone methane sulphonate, 1-3 mg/kg i.v., abolished or reduced photically-induced myoclonic responses for 1.5-6.5 h in baboons, *Papio papio*, without producing signs of acute neurological toxicity.

YG 19-256 is an indenopyridine derivative (figure 1) that inhibits aggressive behaviour in rodents and primates without producing generalized sedation[2,3]. Preliminary test in mice indicate that YG 19-256 protects against the tonic-extensor component of electro-shock induced convulsions (ED 50=25 mg/kg, i.p.), but not against seizures induced by i.v. pentylene-tetrazol[4]. We are reporting that YG 19-256, at dose levels that do not produce motor signs of neurological toxicity, prevents epileptic responses induced by intermittent photic stimulation (IPS) in baboons, *Papio papio*, from the Casamance region of Senegal that spontaneously show photosensitive epilepsy[5,6].

Methods. Experiments were performed in 5 baboons that were moderately or highly photosensitive (i.e. they responded to IPS with generalized myoclonus that was stimulus-limited or self-sustaining, or with a full tonic-clonic seizure). Animals were chronically implanted with epidural electrodes to permit artefact-free EEG recording, and were seated in a primate chair for each acute experiment with a standardized exposure to IPS before, and at fixed intervals from 15 min to 6.5 h after, administration of YG 19-256. In 2 animals the natural syndrome of photically-induced responses was enhanced by the prior administration (175 min earlier) of DL-allylglycine, 180 mg/kg, i.v.[7]. YG 19-256 was administered i.v. as the methane sulphonate, dissolved in sterile saline.

Results. Baboons remained behaviourally alert after YG 19-256, 1-3 mg/kg, but with diminished teeth-baring responses to threatening gestures. Mydriasis and some slowing of EEG background rhythms were noted 3-10 min after YG 19-256, 3 mg/kg. This slowing was maximal after 10-60 min. Motor signs of neurological toxicity of the kind observed after hydantoin or carbamazepine (e.g. nystagmus and ataxia)[7] were not seen at any time after YG 19-256.

In 2 baboons showing generalized myoclonus, but not seizures, in response to control rests with IPS, YG 19-256, 1

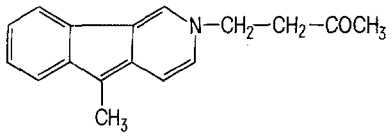

Fig. 1. Structural formula of YG 19-256, 4-(1,3,4,9b-tetrahydro-5-methyl-2H-indeno [1,2-c] pyridine-2-yl)-2-butanone.

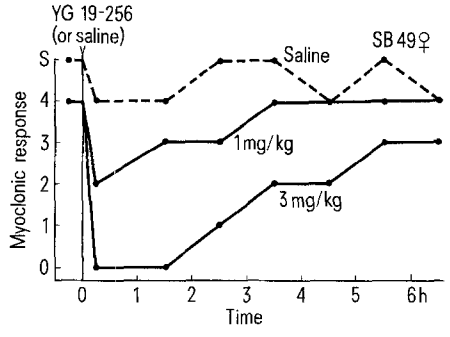

Fig. 2. Graph showing the effect of YG 19-256, 1 or 3 mg/kg i.v., on epileptic responses to intermittent photic stimulation (IPS) in a highly photosensitive baboon (SB 49).
Abscissa: time after the injection of saline or YG 19-256. Ordinate: Response to standardized test with IPS, graded as: 1 = myoclonus of eyelids during IPS; 2 = myoclonus of muscles of face and neck during IPS; 3 = myoclonus involving all the trunk and limbs during IPS; 4 = myoclonus continuing after IPS is terminated; S = tonic clonic seizure.

or 2 mg/kg, reduced the IPS-induced EEG spikes and waves for 2–3 h and abolished the myoclonic responses for 3–6 h. In the most photosensitive baboon (which consistently showed self-sustaining myoclonic, or seizure responses to IPS) YG 19-256, 1 mg/kg, prevented self-sustaining responses to IPS for 2.5 h, and YG 19-256, 3 mg/kg, abolished myoclonic responses for 1.5 h, and prevented self-sustaining responses for 6.5 h (figure 2).

Testing with IPS 5–10 min after YG 19-256, 3 mg/kg, in the 2 baboons pretreated with DL-allylglycine 175 min earlier, instead of the seizures or self-sustaining myoclonic responses expected 3 h after DL-allylglycine, myoclonic responses were found to be absent in 1 baboon and reduced to stimulus-limited responses in the other.

The preliminary studies in rodents and these experiments in baboons indicate that YG 19-256 possesses an unusual spectrum of activity as an anticonvulsant. Other drugs that are effective against maximal electroshock in rodents (e.g. diphenylhydantoin and carbamazepine) are approximately equipotent in rodents and primates and produce marked acute neurological toxicity in the baboon at doses that block self-sustaining myoclonic responses[7], whereas YG 19-256 is more potent as an anticonvulsant in the baboon than in the rodent and has little acute neurological toxicity.

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The effect of piroxicam on platelet aggregation

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Summary. Piroxicam inhibited aggregation of human and dog platelets caused by collagen, but not by adenosine diphosphate (ADP). Release of platelet ADP was inhibited by piroxicam.

Non-steroidal anti-inflammatory (NSAI) agents inhibit collagen-induced platelet aggregation by interfering with the release of platelet constituents[1]. We report here the effects of piroxicam, a new NSAI agent[2], on aggregation of animal and human platelets.

Methods. Platelet-rich plasma (PRP) was prepared[3] from fasted humans and beagle dogs. Platelets were counted in whole blood[4]. Collagen was prepared as a crude suspension of minced rabbit tendon[5,6], and is referred to as tendon extract (TE). Platelet aggregation was studied at room temperature (20 °C) using a modification[7] of Born's turbidimetric method[8]. For in vitro experiments, piroxicam (0.5–100 μM) or 0.154 M NaCl solutions were added to PRP samples from 5 humans 10 min before addition of adenosine diphosphate (ADP) or TE. Concentrations of drugs are final concentrations in plasma. Minimum (20%) inhibitory concentrations (IC_{20}) were calculated by regression analysis. For in vivo experiments, a single oral dose of piroxicam, 2 mg/kg, was given to 5 dogs; platelet responses to ADP (10 μM) and TE, platelet counts, and release of platelet ADP[3] (3 dogs) were determined 24 h prior to and 1, 2, 4, 24, 48 and 72 h after administration of drug.

Results. Piroxicam, 1–100 μM, inhibited TE-induced aggregation of human platelets (IC_{20} = 3.9 μM); ADP-induced platelet aggregation was not affected by piroxicam 100 μM. In dogs piroxicam had no effect on ADP-induced platelet aggregation or platelet count. TE-induced platelet aggregation and release of platelet ADP were inhibited 1 h after oral administration of piroxicam to dogs and for 48–72 h thereafter (figure).

Discussion. The fact that ADP release from dog platelets in response to TE was diminished after oral administration of piroxicam suggests that, like other NSAI agents[1], piroxicam interferes with the release of platelet constitutents. Piroxicam did not inhibit primary ADP-induced platelet aggregation, which is independent of platelet release[9], but it inhibited TE-induced aggregation of human platelets at a concentration 1/60 that reported for aspirin (IC_{20} = 230 μM)[10].