remainder of the interval before the next shock. This excitatory action was readily abolished by intravenous injection of 32 mg of sodium pentobarbital (Fig. 1*C*).

In addition to this relatively direct action on the LGN, reticular stimulation improved the temporal resolution of a geniculate unit in response to intermittent light (Fig. 2). The data for each histogram in Fig. 2 required 4 minutes of recording time, the recordings following each other immediately in the order *A*, *C*, *B*, and *D*, respectively. The dark-adapted cat's eye was stimulated by intermittent flashes of fixed intensity. A geniculate neuron was able to discharge spikes in response to each flash for frequencies up to 24 cy/sec. At 32 cy/sec (Fig. 2*A*) the unit could no longer follow each flash, frequently failing to discharge. This can be readily appreciated from the fact that the total number of spikes discharged over the 2.5 minutes of stimulation was 1294, in contrast to the total number of flashes, that is, 32 cy/sec × 150 sec = 4800. The presence of a peak at approximately 25 msec after the end of the flash indicates the correlation between the light stimulus and the response. When the stimulating shocks were applied to the midbrain reticular formation in synchrony with the end of each flash, the ability of the unit to respond to the high frequencies of flash was greatly improved (Fig. 2*B*). Not only is there a great increase in the total number of spikes but also spikes are more sharply restricted to a particular phase of the flicker cycle.

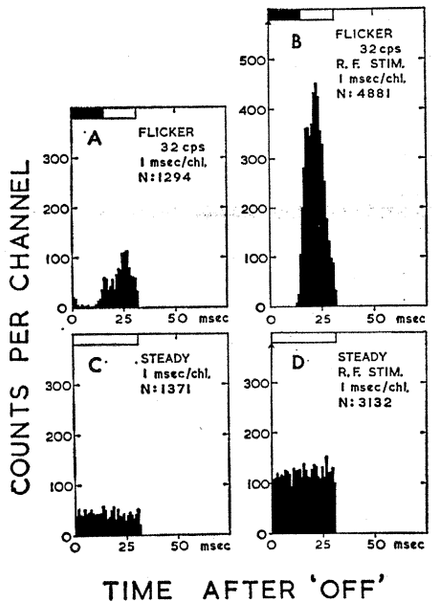

Fig. 2. Effect of reticular stimulation upon responsiveness of single geniculate neuron to intermittent light stimulation. Horizontal black and white bars stand for light off and light on, respectively. By means of a scaler-analyzer channel width of 1 msec, a total of 4800 stimulus cycles were analyzed, each having a duration of 1/32 second. Ordinates represent counts per channel and abscissae time after end of flash (recycle pulse). *N* means total number of spikes analyzed during 2.5 minutes. Arrows indicate stimulation of midbrain reticular formation. *A*, Poststimulus time histogram with only flicker stimulation. *B*, Poststimulus time histogram with flicker stimulation and single-shock stimulation of midbrain reticular formation. *C*, Unitary activity to steady illumination without reticular stimulation. *D*, Unitary activity to steady illumination with reticular stimulation.

Under steady illumination (half intensity of flickering light) the effect of midbrain stimulation was to raise the mean rate of discharge of the geniculate neuron without any special correlation between the stimulating shock and the time of occurrence of spikes (Fig. 2*D*), as compared with Fig. 2*C* in which no reticular stimulation was used.

In evaluating these results two obvious sources of error need to be excluded. First, the effect of the direct spread of stimulating current from the midbrain to the LGN is unlikely to be significant, since the effect long outlasts the duration of the shock. Furthermore, as shown in Fig. 2*D*, there is no correlation between the time of occurrence of the shock and the discharge of spikes. Second, there is also the possibility that midbrain stimulation antidromically excites optic tract axons, thus affecting the geniculate neurons after the manner of an axon reflex. This possibility is excluded because the direct recording from single optic tract axons has failed to reveal any evidence that they are activated by stimulation of the midbrain reticular formation, at least from the stimulating site used in these experiments. This finding also excludes the possibility that centrifugal influences from the midbrain to the retina (*5*) are indirectly affecting the LGN by a subsequent centripetal discharge from the retina.

While the effects of midbrain stimulation reported here have all been excitatory as far as geniculate neurons are concerned, the possibility that inhibitory influences also occur is not excluded, since the number of units so far tested is only small (*6*).

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6. This research was aided by grants from the National Health and Medical Research Council of Australia and from the Postgraduate Medical Foundation, University of Sydney, of which I am a fellow.

30 October 1962

Citrus Flavonoid Complex: Chemical Fractionation and Biological Activity

Abstract. *A study was made of the anti-inflammatory activity of the fractionated components of a citrus flavonoid complex. Several highly active components, distinct from hesperidin and naringin, were isolated and tested for anti-inflammatory activity. A method for evaluation of this biological activity is recommended.*

Following Szent-Gyorgyi's original observations of the effects of his vitamin P or citrin preparations (*1*), investigations by the many workers produced an experimental and clinical literature of contradictory thought and observations that culminated in the recommendation that the designation vitamin P be abandoned (*2*). Nevertheless, work in this field has continued and the term "bioflavonoids" was coined to denote those flavonoid compounds having biological activity.

In view of the increasing number of reports of the therapeutic utility of a water-soluble citrus flavonoid complex (*3*) prepared from citrus (mixed orange and grapefruit) peel and pulp (*4*) which have appeared continuously since 1948, we undertook to determine

Table 1. Anti-inflammatory (A.I.) activity of components of a bioflavonoid complex. Test substances were administered orally 2 hours prior to challenge.

Test substance	ED_{25} (mg/kg)	Potency (A.I. units/g)
Hesperidin*	Inactive	0
Naringin*	Inactive	0
Nobiletin	20	50
Pentamethoxyflavone	20	50
RS–1	3	333
Hydrocortisone phosphate (reference)	13.5	74

* Tested at doses between 200 and 400 mg/kg.

the nature and biological activity of its components.

The citrus flavonoid complex was separated into three fractions by differential solubility in methanol and ethyl acetate.

One hundred grams of citrus flavonoid complex (*3*) was added to 1 liter of methanol, stirred for 1 hour at room temperature, and filtered on a sintered glass Buchner funnel. The insoluble material was washed with 100 ml of methanol, and when dried in a vacuum at 60°C resulted in 35 g of dark brown powder (fraction I). The combined methanol filtrate and washing, after concentration to approximately 300 ml under reduced pressure, was added to 5 volumes of ethyl acetate. After stirring for 15 minutes the mixture was filtered; the insoluble material after it had been washed with 100 ml of ethyl acetate and dried in a vacuum at 60°C, was a light brown powder weighing 29 g (fraction II). The combined ethyl acetate filtrate and washings were concentrated under reduced pressure to approximately 50 ml which, when dried in a vacuum at 60°C, was a yellow powder weighing 32.7 g (fraction III).

Each of the fractions and the untreated flavonoid complex were assayed for anti-inflammatory activity by the modified (*5*) method of Ungar (*6*). Sixty-five percent of the anti-inflammatory activity of the starting material was concentrated in fraction III (*7*). When inflammation was produced by either inflammatory exudates or leukotaxin, the citrus flavonoid complex displayed a broader inhibitory potential than either cortisone or ACTH (*8*).

Chromatography on Whatman No. 3MM paper with the mixture of four parts of butanol, one part acetic acid, and five parts water (BAW) as the aqueous phase separated fraction III into six components which fluoresced in ultraviolet light with R_F values of 0.12, 0.18, 0.39, 0.54, 0.71, and 0.84. Only the component at R_F 0.84 gave a typical flavanone reaction when sprayed with the sodium borohydride reagent of Eigen (*9*).

Fraction III was then fractionated to yield hesperidin, naringin, and relatively small amounts of 5,6,7,8,3′,4′-hexamethoxyflavone (nobiletin), a pentamethoxyflavone isomeric but not identical with tangeretin, and an unidentified component (RS–1) with reducing properties, and an R_F 0.71 in BAW.

Increased capillary permeability is the basic initial manifestation of inflammation, and practically all the methods devised for measuring inflammation have been based on the loss of plasma into the inflamed tissue. The various techniques have been discussed by Ungar (*10*) who has presented a new method of bio-assay based on the direct measurement of the edema formation characteristic of acute inflammation. This method, which is reproducible and reliable for the quantitative evaluation of anti-inflammatory activity, was used to assay the components of fraction III (Table 1). One unit of potency (ED_{25}) is the weight of test substance per kilogram weight of guinea pig producing a 25-percent reduction of edema. The results demonstrate that there are in citrus peel extracts factors acting to inhibit increased capillary permeability, that these factors are distinct from hesperidin or naringin, and that the amount varies according to the methods of extraction and preparation employed.

Unfortunately, the designations "bioflavonoids," "citrus bioflavonoid complex," "citrus bioflavonoids," and similar terms are applied interchangeably in the experimental and clinical literature to materials of diverse origin, purity, identity, and biological activity. Thus even in a critical review (*11*) the implication has been that results obtained with any flavonoid are applicable to all flavonoids as a class. Evaluation of the biological activity of flavonoid preparations by the procedure of Ungar (*10*) would differentiate between them according to anti-inflammatory activity and could add considerably to the clarification of the utility of "bioflavonoids" in humans.

However, further work is necessary to elucidate the relationship of the demonstrated effects of biologically active flavonoids in laboratory animals to their clinical effects in humans, particularly in view of the species differences in absorption and metabolism of these substances (*12*).

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26 October 1962

Meteorite with Unique Features

Abstract. *A brief account of the discovery in Luzon, Philippines, of a large meteorite that does not fit into any of the currently used classifications is presented; together with results of preliminary studies of its unprecedented structure, specific gravity, and multiple magnetic polarity. Its probable terrestrial age is also discussed.*

A 1955-lb meteorite of unique structure has been recovered from a remote location in the Bondoc peninsula on southern Luzon Island in the Philippines (Fig. 1).

The meteorite was located during our visit to Manila in 1958 through information obtained from the National Bureau of Mines in Manila. The Bureau had received a small sample, but was not interested in pursuing an investigation. The specimen, together with meager information, was then turned over to us; since that time we have been working through a local field party for its recovery.

The first sample was a badly oxidized nickel-iron nodule weighing 684.1 grams with a specific gravity of 7 plus. Later samples from the field ranged from 3.26 to 6.35 in specific gravity with an average of 3.94. All local geologists and mining men called them "low-grade iron ore" and not meteoritic. It was felt that this was a very unusual meteorite and efforts to recover it were intensified. These were successful, and the meteorite arrived in Sedona, Arizona, on 10 August 1962 (Fig. 2).

A section measuring 71.2 by 43.8 cm was cut from near the small end of the generally oval-shaped mass. This cut