The Analgesic Action of Teropterin[1]

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In 1947 Farber and his associates (*1*) indicated that teropterin, when administered to patients suffering from various forms of cancer, made it possible in some instances to reduce the amount of analgesia required. This indicated that teropterin possessed a certain amount of pain-relieving activity. Lehv, *et al* (*2*) stated categorically that "Our clinical observations indicate that the drug is nontoxic in the dosage given. Pain was relieved in most instances, if not all, by the use of teropterin. This obviated, in the main, the necessity for further use for opiates with their concomitant depressive effect."

These clinical observations on the analgesic property of teropterin were of interest in our laboratory, and we decided to prove or disprove the pure pain-relieving activity of this drug.

Twelve experiments on premedical students were performed, using a modified Wolff-Hardy-Goodell technique. Each one of the subjects received a 20-mg dose of teropterin injected intramuscularly. Neither the operator of the pain threshold apparatus nor the subject was cognizant of the nature of the drug that was injected, since all doses were administered by a third individual.

A definite rise in the pain threshold response was observed 15 min following the injection of 20 mg of teropterin. On an average, the peak of the effects were reached in 70 min and lasted for 155 min. Teropterin produced a 6.6% rise in pain threshold when the peak of the effects were reached. In each instance the experimental data showed that the effects were always in the same direction. This fact made it clear to us that teropterin was actually producing a true analgesic effect.

The results on 12 subjects definitely indicate that teropterin causes analgesia as interpreted by a rise in pain threshold in man. This confirms the clinical observations thus far reported. Contrary to the sense of well-being and some slight euphoria as was noted in those patients with cancer who received teropterin, we did not observe any of these effects. Nausea and other subjective symptoms were also lacking.

Teropterin possesses true analgesic action when tested on the normal human subject. This activity should be of value in reducing the amount of sedation needed when teropterin is used clinically.

References

1. Farber, Sidney, Cutler, Elliott C., Hawkins, James W., Harrison, J. Hartwell, Pierce, E. Converse, II, and Lenz, Gilbert G. *Science*, 1947, **106**, 619.
2. Lehv, S. P., Wright, L. T., Weintraub, S., and Arons, I. *N. Y. Acad. Sci.*, 1948, **10**, 75.

[1] Teropterin was kindly furnished by the Lederle Company, Pearl River, New York.

Flow in a Thin Glass Capillary as Affected by Wetting the Exterior of the Capillary[1]

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A review of pertinent literature has revealed widespread evidence that the outermost monolayer of molecules at the phase boundary of a liquid induces an orientation extending into the body of the liquid for many molecular lengths (*1*). The most reliable examples involve a range of orientation from a few tens of Angstrom units to a few thousand. The experiments of Nutting (*3*), however, pointed to an immobile layer of much greater depth.

Nutting found that the flow of crude petroleum oil through a narrow thin-walled glass capillary was appreciably slowed (6.8%) when the *outside* of the capillary was surrounded with water. He accounted for this by postulating an immobile layer of oil on the inside of the tube no less than 65,000 A thick. Kaminski, working in these laboratories and following the method outlined by Nutting, obtained comparable results (*2*).

It was apparent, however, that the effect could have been due to variations in temperature, since the temperature coefficient of viscosity of the medicinal paraffin oil used by Kaminski was such that the flow would have

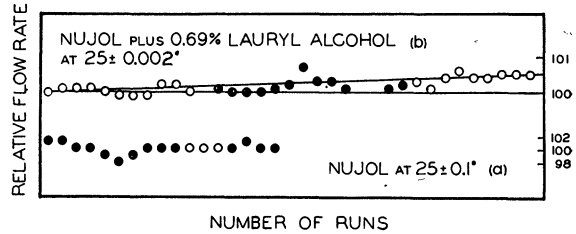

FIG. 1. Relative flow rate plotted against the number of passes through the capillary in (a) Series 1, and (b) Series 3. Open circles refer to passes when the outside of the capillary was dry; solid circles when the capillary was surrounded by water.

increased 7%/°C. Nutting's effect could be accounted for by the oil's being a degree warmer when not surrounded by water, and Kaminski's could be accounted for similarly by variations of a degree or two. This might well have occurred if the apparatus or the oil had been exposed to radiant energy during a measurement, or if the room temperature had risen just before a measurement. The particularly marked retardation in the flow of crude petroleum reported by Nutting and confirmed by Kaminski might thus be explained by the strong absorption this oil shows in the near infrared. Either of these variations would have warmed the dry capillary or reservoir of oil more rapidly than the capillary surrounded by a relatively large mass of water, and would then have led to a faster flow in the dry tube than in the wet.

[1] This work was done under contract between the Office of Naval Research and Stanford Research Institute.

Series 1: In order to evaluate the effect of temperature variations, Kaminski's apparatus was transferred to an air thermostat whose temperature varied less than 0.1°. It seems most unlikely that moving the apparatus into the thermostat could have changed any condition other than temperature, which may have been responsible for the Nutting effect observed by Kaminski. Deviations in flow rate up to 1.5% from the mean value were observed, but they showed no discernible consistent change after the capillary had been immersed in distilled water overnight, or after it had been allowed to dry out again for 3 days. The data are plotted in Fig. 1a.

Series 2: A more precise control of temperature was obtained by immersing the jacket containing a capillary in a water thermostat at 25° ± 0.002°. The internal diameter of this capillary was 0.747 mm. In these experiments, the capillary was made part of a U-tube, enlarged at one point to form a small reservoir, in the manner of an Ostwald viscosimeter. Great care was taken to eliminate possible surface active impurities. The entire apparatus was flamed to incipient fusion while a current of dried filtered air was passed through it. Both entrance tubes were bent downwards and guarded by plugs of glass fiber. The Nujol had stood with 10 per cent of its weight of Florisil (an activated silica) for a week with occasional shaking, and was centrifuged before use.

Thirteen runs were made in the dry capillary, 9 after filling the jacket with water, followed by 5 more after drying again. The flow times varied within 0.4% of the mean value (between 360 and 363 sec) with no indication of a consistent increase during the period of wetting. The experimental errors were magnified somewhat by an uncertain drainage of the measuring reservoir, which was below the capillary in this apparatus.

Series 3: Since a small percentage of a polar long-chain compound might produce an oriented immobile layer under conditions where a nonpolar oil would not, lauryl alcohol was added to make a 0.69% solution. (The Nujol wetted the glass, the lauryl alcohol solution did not.) The flow times relative to the first value, plotted against the number of runs, are shown in the upper plot (Fig. 1b). The radius of the circle represents probable errors in the timing, but does not take into account the variable drainage of the tube. It will be seen that any retardation that may have occurred on wetting the outside of the capillary is less than the random fluctuations (about 0.5%). A small but definite retardation with time of about 0.5% may be seen, however. The film thickness necessary to account for this would be about 0.9 μ, instead of 6.5 μ, which although still high, is more nearly in accord with the observations of others in this general field. It may also be due at least in part to slight clogging of the capillary by traces of suspended matter.

References

1. HENNIKER, J. C. In press.
2. KAMINSKI, A. *Office of Naval Research*, Rep. no. 1. 1948.
3. NUTTING, P. G. *Science*, 1943. 97. 74–75.

Paper Chromatography of Flavonoid Pigments[1]

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Although the use of classical chromatographic adsorption methods for the separation of flavonoid pigments from plant extracts has been reported previously (*3*, *4*, *5*), such methods have not been successful in the separation of microquantities of these compounds. In a search for better methods of examining plant extracts for flavonoid pigments, we have applied the method of paper partition chromatography (*2*) to the problem. This preliminary report deals with the determination of R_f values for 11 flavonoid pigments in chloroform, ethyl acetate, phenol, and n-butanol-acetic acid; the separation of mixtures containing four to six of these pigments; and the use of color developing sprays to locate and identify the pigment zones.

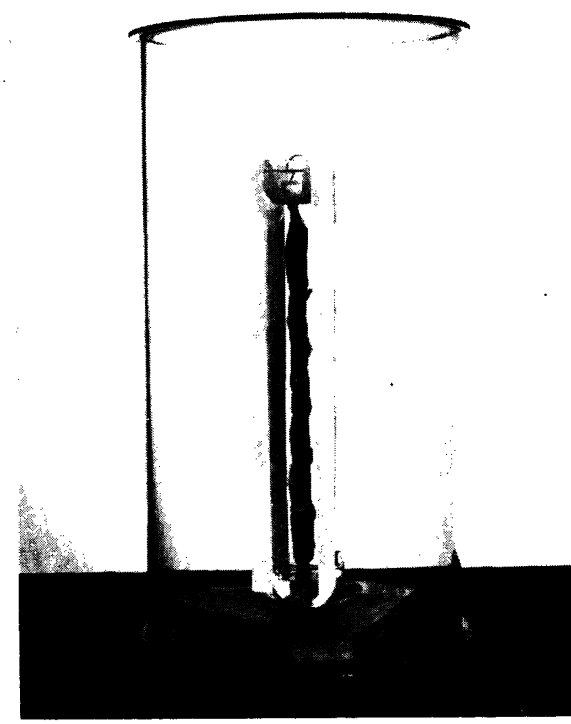

FIG. 1.

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