$$\left.\begin{aligned} CL&: \zeta = e^{i\frac{\pi}{6}}\lambda \\ CR&: \zeta = e^{i\frac{5\pi}{6}}\lambda \\ CF&: \zeta = e^{i\frac{3\pi}{2}}\lambda \end{aligned}\right\} \qquad (2)$$

where e = the base of natural logarithms and λ is a real parametric variable equal to $|\zeta|$. Substitution of Eq (2) in Eq (1) yields

$$\left.\begin{aligned} CL&: dw = |K|(\lambda^3-1)^{-\frac{2}{3}}\, e^{i\frac{\pi}{6}}\, d\lambda \\ CR&: dw = |K|(\lambda^3-1)^{-\frac{2}{3}}\, e^{i\frac{5\pi}{6}}\, d\lambda \\ CF&: dw = |K|(\lambda^3-1)^{-\frac{2}{3}}\, e^{i\frac{3\pi}{2}}\, d\lambda \end{aligned}\right\} \qquad (3)$$

the real value of the radical being intended in each case.

Certain conclusions are warranted from an inspection of Eq (3): (*a*) the radii in question remain rectilinear after the transformation, (*b*) the 120° angular separation between them is not altered by the transformation, and (*c*) the transformed radii are all of equal length. Therefore we may conclude that the point *C* remains centric in the triangle and that the transformation does not alter the angular relation of any line, as it passes through the center, with respect to the points *L*, *R*, and *F*. Since Schwarzian transformations do not alter the topology of isopotential distributions, and the present transformation in particular does not translocate the electric doublet or rotate its axis, it is evident that the manifest potential calculated from the potentials at the apices of the triangle will have the same direction as the axis of the doublet.

The transformation was demonstrated experimentally by preparing an equilateral triangular model 32.5 cm on a side (Fig. 2) from a sheet of conducting material of intermediate resistivity.[2] A centric doublet consisting of two circular poles 2.5 mm in diameter and separated by a distance of 15 mm between centers was drawn on the model with silver ink. The axis of the doublet was inclined at 45° to the horizontal axis of the model. The poles were energized with an alternating current of approximately 125 c/sec. Isopotential lines were mapped out with an exploring electrode by a null technique in which the model constituted two arms of an impedance bridge. A high sensitivity vacuum tube voltmeter was employed as an indicating device. Since no significant amount of phase shift occurred, the mapping procedure was accomplished with considerable precision.

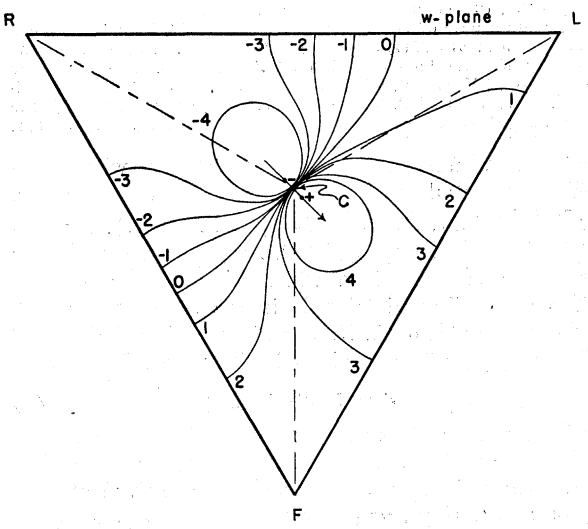

FIG. 2. Isopotential distribution in an Einthoven model of the human body, experimentally determined. The direction of the axis of the doublet is the same as the theoretical case in Fig. 1. Note that the topology of the isopotential distribution in the two figures appears to be the same to the extent that the point *R* remains in the area bounded by the −3 and −4 lines, etc.

The relative potentials at the apices of the model were measured to three significant figures. The manifest potential calculated from these values was directed 44.9° clockwise to the horizontal axis. Because the deviation between this value and the anticipated value of 45° was so small, the experiment appeared to confirm the theory that in the Einthoven model the manifest potential accurately indicates the direction of the axis of the doublet.

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[2] Type 1 Teledeltos paper, General Electric Company.

Surface Activity of Naturally Occurring Emulsifiers

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Recently the addition of emulsifiers or other surface-active agents to foods has led to a discussion of the possible effects of surface activity on normal digestive processes. Before the effects of added emulsifiers can be properly assessed it is necessary to know the level of surface activity resulting from the emulsifiers naturally present. The surface activity of an emulsifier[1] is measured by the change in the tension at an oil-water phase boundary as the concentration of that emulsifier is changed. As far as is known, no systematic study has been made of the boundary tension relationships in systems resembling those appearing during the digestion of fats. In particular, no study has been made of the effects of monoglycerides, bile salts, or fatty acids on oil-water boundary tensions in such systems. Research in this latter field has been started in these laboratories, and the first results of the study are reported here.

[1] The surface activity of any material is measured by the extent to which it is adsorbed at a phase boundary. Highly surface-active materials are strongly adsorbed.

TABLE 1

COMPARISON OF THE SURFACE ACTIVITY OF NATURAL EMULSIFIERS WITH VARIOUS SYNTHETIC SURFACTANTS AT OIL-WATER INTERFACES

Surfactant	Type	Conc wt % external phase	Soluble in oil or water	Interfacial tension 1 min (dynes cm^{-1})	Interfacial tension 20 min (dynes cm^{-1})
Doubly distilled water				24.5	23.6
1-Monopalmitin	Nonionic	1.000	Oil	10.3	10.0
"	"	0.500	"	17.7	16.0
2-Monopalmitin	"	1.000	"	9.9	9.3
"	"	0.500	"	15.8	15.9
1-Monoolein	"	1.000	"	11.0	10.3
"	"	0.500	"	18.6	17.2
Bacto bile salts	Anionic	.500	Water	9.2	6.7
" " "	"	.250	"	12.7	11.0
Sodium cholate	"	.500	"	5.6	4.6
" "	"	.250	"	9.4	8.4
Sodium glycocholate	"	.500	"	9.4	6.7
" "	"	.250	"	10.7	8.7
Sodium laurate	"	.500	"	3.6	1.8
" "	"	.250	"	7.5	6.6
" "	"	.100	"	13.6	12.4
Sodium alkyl sulfate	"	.100	"	3.2	2.1
" " "	"	.025	"	9.9	7.7
" " "	"	.010	"	12.9	10.3
Sodium alkyl benzene sulfonate	"	.100	"	3.9	2.9
" " " "	"	.025	"	7.2	4.6
" " " "	"	0.010	"	9.9	7.0
Dimethylbenzyl alkyl ammonium chloride	Cationic	$>$ 0.025	"	$<$ 0.5	$<$ 0.5
" " " "	"	.025	"	5.7	1.1
" " " "	"	.010	"	8.9	3.5

A method for the measurement of the boundary tension of any system containing surfactants must meet two rigid qualifications: (1) the measurement must be independent of the contact angle between the solution and the measuring device, and (2) sufficient time must be allowed for the diffusion of the surfactant, in equilibrium concentration, to the boundary layer at the freshly formed interfaces. Neither tensiometric nor capillary rise techniques meet these qualifications for oil-water boundary tension measurement in the presence of surfactants.[2] Either the drop-weight method (*2*) or the pendent-drop method (*3*) as modified (*4*) are satisfactory in such systems. In the studies reported here, the drop-weight method for boundary tension measurement has been used primarily. The validity of the results has been checked on several representative systems by measurements with the pendent-drop method. The two methods agreed.

It is instructive to compare the relative surface activity of several different types of surfactants at an oil-water boundary. Data are listed in Table 1 for the interfacial tensions at a cotton seed oil/water interface in the presence of the several surfactants. Double-distilled water, surface tension of 69.5 dynes cm^{-1} at 37° C, was used to make up the aqueous phase. A refined bleached cottonseed oil (CSO), IV = 116, AV = 0.5, was used as the oily phase. All measurements were made at body temperature (37.0° C).

All these surfactants are water-soluble, with the exception of the monoglycerides. The concentration listed in Table 1 refers to the concentration of surfactant in the phase surrounding the forming drop. To insure that concentration changes that are due to adsorption at the drop surface and to partial solubility in the drop-forming phase were minimized, the surfactant solution was used always as the phase surrounding the drop.[3]

These surfactants and emulsifiers at concentrations below 0.5% are grouped into three levels of surface activity. The synthetic materials commonly used as wetting agents, such as the alkylbenzene sulfonates, the alkyl sulfates, or the dimethylbenzyl alkyl ammonium chlorides, are by far the most effective surfactants in the water/oil system. Of intermediate activity are the bile salts and sodium laurate; the monoglycerides, the two monopalmitins, and monoolein compose the third and least surface-active group of the materials studied. It should be emphasized that, of the materials listed in Table 1, monoglycerides are the least surface-active. For example, mixed bile salts, or sodium cholate, or sodium glycocholate are far more effective as surfactants. In addition, it has been established that bile salts form a complex with fatty acids (*5*). Such a complex would be expected to show even greater surface activity at an oil-water boundary than do the bile salts alone.

[2] A recently published work (*1*) showed the capillary rise method to be completely unreliable for interfacial tension measurements in the presence of surfactants.

[3] The drop of the aqueous phase was run into the oil solution of monoolein, whereas the oil drop was run into water solutions of the other surfactants. In an equilibrated system, the boundary tension is independent of the manner in which the drop is formed.

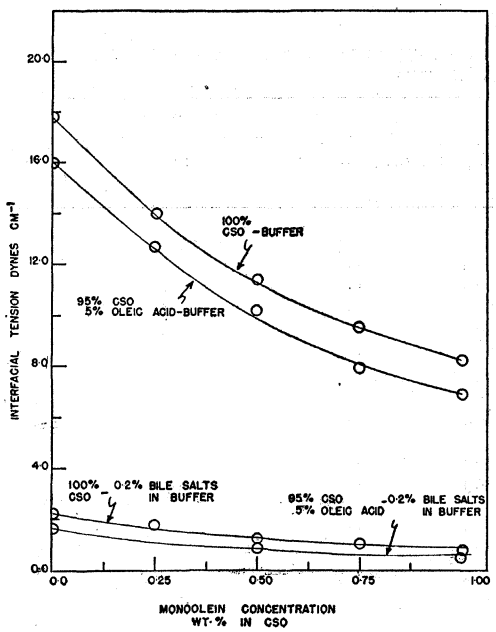

FIG. 1. Effect of monoolein concentration on boundary tensions in systems of CSO and 95% CSO-5% oleic acid in contact with citrate-phosphate buffers at pH 6.0 with and without an added 0.2% bile salts. All measurements were made at 37° C.

The conditions under which the above measurements were made, with the exception of the temperature, are different from digestive conditions. Most fat digestion takes place in the upper part of the small intestine. To approximate the conditions in this region of the intestine during fat digestion, one must consider the pH and bile salt concentration of the aqueous phase, along with the fatty acid content of the fat. In a normal person, the pH in the duodenum is very nearly 6.0 (*5*) during the digestive process. From the available physiological data (*6, 7*) an estimate within the lower range of the bile salt concentration in this region of the intestine would be about 0.2%. Normally the bile salt level would be much higher than that figure.

Work in these laboratories has established that the fatty acid content of digesting fat ranges up to 30% by weight. For the present studies, a concentration of 5% for the free fatty acid was chosen as the minimum expected under digestive conditions.

In Fig. 1, data are shown for the effect of increasing monoglyceride concentration on the interfacial tension of a mixture simulating what might be found in digesting fat—i.e., fat, fatty acid, monoglyceride, bile salts, and buffer solution. For comparison, data are also shown for the effect of monoglyceride on the boundary tension in systems of CSO, 95% CSO-5% oleic acid, and fatty acid-free CSO in the presence of bile salts. A very low interfacial tension is observed in the two systems containing bile salts.[4] It is evident that bile salts are by far the most effective surfactants in a system simulating digesting fat. It is also evident that increasing the monoglyceride concentration above 0.50% cannot result in any appreciable adsorption of the added emulsifier at the oil-water interface. In the absence of bile salts, monoglyceride is surface-active. At a pH of 6.0, fatty acid is practically inert.

The boundary tension of triglyceride-water systems has been found to be quite sensitive to pH, particularly in the presence of fatty acids (*9–11*). The pH range in the intestinal tract ranges from 5.0 at the pylorus to 8.0 at the ileocecal valve (*12*). Boundary tension data were obtained over this pH range for systems of CSO and 95% CSO-5% oleic acid against a buffer solution and against the buffer solution with 0.2% bile salts added. These data are plotted in Fig. 2.

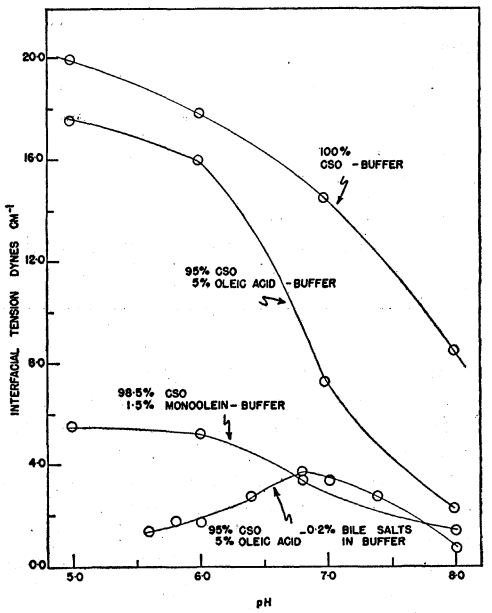

FIG. 2. Effect of pH on oil-water boundary tensions in systems of monoolein, oleic acid, CSO, and bile salts. Citrate-phosphate buffers used and all measurements were made at 37° C.

In general, increasing the pH of the aqueous phase lowers the boundary tension at the oil-water interface. However, with the combination of bile salts and fatty acids an anomaly is observed. The boundary tension rises to a maximum at pH 6.8. Apparently the complex formed between fatty acids and bile salts becomes less surface-active as acid soaps are formed. Notice that at the pH of digesting fat, the combination of bile salts and fatty acid is more effective as a surfactant in CSO than 1.5% of monoglyceride.

A system simulating that occurring during fat digestion is characterized by a very low oil-water boundary tension as a result of the quantities of natural emulsifiers, bile salts, and fatty acids normally present. The low boundary tensions are observed even without monoglycerides, also normally present. In fact, boundary tensions are so low that large quantities of mono-

[4] The low value observed in the system simulating digesting fat is in agreement with the findings of Frazer *et al.* (*8*). These authors state that an interfacial tension on the order of 0.5 dyne cm^{-1} is required for fat absorption.

glyceride could be added without significantly raising the normal levels of surface activity in such systems.

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The Anticonvulsant Activity and Toxicity of Methylparafynol (Dormison®) and Some Other Alcohols[1]

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Although a number of effective drugs are currently available for the control of the human convulsant state (epilepsy), the occurrence of toxic manifestations attributable to these agents stimulates the search for new compounds with low order of toxicity. A good anticonvulsant drug should suppress seizures without hypnosis and, if possible, without untoward effect upon other physiological processes such as hematopoiesis or liver function. Effective use of the barbiturates, hydantoins, or oxazolidines may often be limited by inordinate somnolence, gastrointestinal irritation, personality change, skin eruptions, bone-marrow depression, liver damage, gum hypertrophy, or photophobia.

In October 1951, Margolin, Perlman, Villani, and McGavack (*1*) reported the hypnotic activity of the unsaturated tertiary carbinol, 3-methyl-pentyne-ol-3, which has been used clinically as a soporific under the generic name methylparafynol (Dormison®). This compound, which was shown to have a hypnotic activity in man of about 40% relative to phenobarbital and pentobarbital, was reported to have remarkably low toxicity. Clinical studies revealed no liver, kidney, or bone-marrow damage. No respiratory depression or addiction was observed. Since a number of alcohols, notably isopropyl, have in recent years been studied in our laboratory (*2*), the possible anticonvulsant action of methylparafynol seemed apparent to us. In a preliminary, unpublished study, using the method of Merritt and Putnam (*3*), we found that this pentyne alcohol elevates the cortical threshold for electrically induced seizures in rats. With a dose of 250 mg/kg, the cortical threshold is raised an average of 70.6%. In May 1952, we reported (*4*) the ability of methylparafynol to alter the convulsion pattern of supramaximal stimulation in rats. We found that the duration of anticonvulsant action is in excess of 8 hr, that the action of phenobarbital is potentiated, and that the drug is capable of controlling seizures in human epileptics.

Clinical trials of methyparafynol by the staff of the Stanford Neuropsychiatry Department, however, were suspended after 6 weeks when two of six epileptics under treatment developed strongly positive (3 and 4 plus) cephalin flocculation tests. One week after discontinuation of the alcohol, these tests were negative. A seventh patient, a 13-year-old girl under the care of a private pediatrician, developed a 2 plus cephalin flocculation test during the first 2 months of treatment; but this test reverted to negative under continuing methylparafynol therapy, which was not abandoned since this was the only agent capable of preventing her grand mal seizures. Since, however, clinical laboratory evidence of hepatotoxicity had become apparent in the adult patients, chronic feeding experiments were performed in rats. Five control rats and 10 rats given 0.175% methylparafynol in the drinking water were studied for 4 months. No significant difference was found in growth rate, or in food and water consumption. At the end of each month, a control and a treated animal were sacrificed by decapitation, and the livers were examined histologically by Lelland Rather, of the Stanford Pathology Department. There was no apparent difference in nuclear volume; there was a slight but definite diminution of cytoplasmic basophilia in the hepatic cells of the methylparafynol-fed rats. Loss of cytoplasmic basophilia may under some, but not all, circumstances indicate diminution of ribonucleic acid (*5, 6*). The metabolic and clinical significance of such a change remains to be determined. It might conceivably be associated with changes in the protein production of the liver cell. In order to determine whether the presence of the pentyne alcohol in the blood might produce a "false-positive" cephalin flocculation, this test was performed after the addition of methylparafynol to blood samples from four normal human subjects. Even with excessive concentrations (400 mg/100 ml) of the alcohol, these sera all yielded negative cephalin flocculation tests. It would appear, therefore, that methylparafynol is possibly capable of producing alteration of liver function.

Suspecting that the triple bond in methylparafynol might be responsible for the possible hepatotoxicity, we have undertaken the investigation of a number of saturated secondary and tertiary alcohols. These are listed in Table 1, where their effects are compared with those of methylparafynol, ethanol, and the established

[1] This work was supported, in main, by the Stern Fund for Research in Anticonvulsants and, in part, by Schering Corporation.

[2] We wish to thank Donald Scanlon and Marilyn Enger for their help in the performance of these experiments.