Table 1. Striking impulse and resultant head acceleration at which concussion occurred [1 lb (0.45 kg)].

Monkeys concussed (%)	Acceleration (g)	Impulse (lb/sec)
10	10–14	0.045– .075
50	100–103	.415– .437
90	865–869	2.994–3.026

sponse phenomena were correlated with the occurrence or nonoccurrence of concussion by use of Spearman's rank-correlation method, a nonparametric type of statistical-analysis tool. The results indicated that the experimental values for magnitude of impact force, tangential velocity of the head, and changes in intracranial pressure could not be significantly correlated with the production of concussion by an occipital blow to the freely moveable head of the monkey under such conditions. On the other hand, the peak velocity of the impacting piston and its kinetic energy correlated ($P \leq .001$), while the total impulse of the blow and the peak value of the linear acceleration of the head correlated significantly ($P \leq .01$). We should emphasize that these correlations hold true for impact phenomena that occur within the duration limits of 1 and 10 msec; impacts and head loading for other time regimes have not been explored.

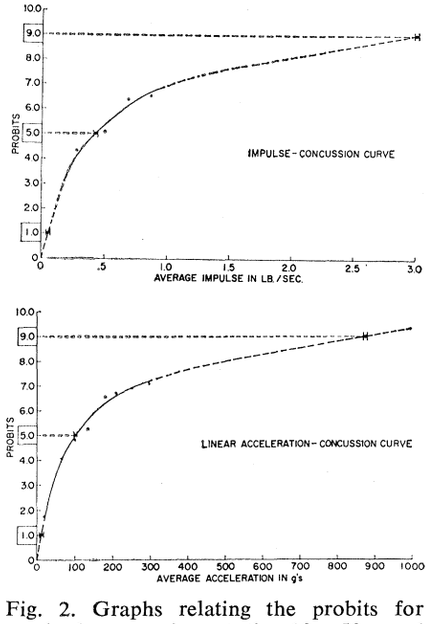

Fig. 2. Graphs relating the probits for cerebral concussion at the 10-, 50-, and 90-percent levels to the average impulse in pounds second (lb. sec) and to the average acceleration in multiples of gravity (g). Note the wide range of values between the 10- and 90-percent levels. The two short vertical lines beside the heavy dot at each of the three levels indicate one standard deviation about a mean.

Of all the statistically significant physical indices of concussion, the magnitude of impulse was the most satisfactory; it could be easily measured with a single force transducer and derived independently of consideration of mass and of other dimensions of either the object struck or the striking object. Among the head-response indices, only the linear acceleration showed significant correlation with concussion.

In order to determine the relation between the striking impulse, responsive head acceleration, and probability of occurrence of concussion, a probit transformation was conducted. This method, commonly used in toxicology to calculate the LD_{50} of drugs, enabled the construction of two graphs relating impulse and acceleration, respectively, to concussion occurring in 10, 50, and 90 percent of monkeys under our conditions (Fig. 2). Our current experiments are being conducted at the 50-percent level in order to obtain maximum information and confirmation of this model.

That the range of impulse applied, as related to concussive probability (Fig. 2), is wide suggests that, whatever the mechanics of concussion may be, the physiological response is not an all-or-none type of phenomenon strictly localized in one area of the brain. This range in values for striking impulse and resulting head acceleration at which concussion occurred (occipital blows, head freely moveable, animal seated) appears in Table 1. The values in Table 1 indicate a range of one standard deviation about a mean value and are rounded off to the nearest unit for acceleration. Again we stress that these values are true only when the duration of the impact phenomena is between 1 and 10 msec.

The graphs in Fig. 2 are used as "dosage curves" would be; they enable us to employ in several ways, with some degree of confidence, an experimental analogue of cerebral concussion in the monkey. For example, we are systematically studying two major fields: (i) the effects of blows to different parts of the head and of blows to each region under different conditions of fixation and protection of head and neck; initial results indicate that reduction of movement between the head and neck (but *not* head fixation) significantly protects against concussion and raises the tolerance of the animal to head impact; (ii) general physiological, electrophysiological, biochemical, and morphological (including ultrastructural) effects to determine functional and pathological changes during and after concussion.

This experimental model may be of use to other workers wishing to study this problem, but hitherto inhibited by lack of a reproducible system for testing hypotheses (*1*). Perhaps the greatest remaining difficulty with such a model is evaluation of the state of consciousness of animals subjected to trauma under anesthesia. Reproducible control of degrees of anesthesia is not possible; thus, determination of the relative significances of anesthesia and concussion in a reduced state of consciousness is very difficult. We would welcome suggestions regarding this aspect.

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3 May 1966

Myeloma Cells and Immunoglobulin Formation

The report of Fahey *et al.* (*1*) that human lymphoid cells derived from "Burkitt's tumors" synthesize immunoglobulins in vitro is important for many reasons. The culture of these cells in various media and in large quantities will permit critical studies of the synthesis of these proteins. Further, it may be possible to provoke production of specific antibodies.

The relationship of the anatomy and physiology of these cells to immuno-

globulin synthesis should clarify the relationship of various classical types of lymphoid cells.

The synthesis of immunoglobulins by cultured lymphoblastoid cells derived from the buffy coats of patients with myeloid leukemias, lymphosarcomas, and Hodgkin's disease has been demonstrated in our laboratories (*2*). Over 50 cell lines originated from 26 patients are available for study. In contrast, no immunoglobulins have been detected in cell lines derived from malignancies of nonhemopoietic tissues.

We would appreciate the opportunity of obtaining blood samples from patients with multiple myeloma who have plasma cells in their peripheral blood.

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Protein Conformations in Biological Membranes

The conclusions of Maddy and Malcolm (*1*), based upon infrared spectroscopy of dried erythrocyte membranes and optical rotatory dispersion of solutions of membrane proteins, are unwarranted for the conformations in vivo of proteins in biological membranes. Their quotation from my book (*2*) and their added remarks do not convey the points that I propose an extended β-type conformation only for the primarily structural proteins of hydrated membranes in vivo (decidedly not for all the proteins, nor in dried membranes), and that this conformation is stabilized by interactions with both the lipid phase and the aqueous phase of the membrane (involving hydrophobic interactions as a major component). According to this treatment, one may expect a large decrease in the amount of extended conformation upon either dehydrating the membrane or greatly reducing its lipid content. In fact I discuss in detail (*2*) the total conversion of the extended conformation of the structural proteins to a globular conformation as a result of reduction or loss of the lipid phase under certain conditions, and the reversible partial conversion to the globular conformation during membrane transformations.

In the present state of our knowledge it is a step backward to conclude that findings regarding the conformations of proteins in dried membranes set guidelines for future studies and for theorizing concerning the conformations in vivo of membrane proteins. It would be interesting to know the basis for the authors' statement that air drying of a membrane should not be expected to reduce the amount of β-conformation present. For such an assertion to carry weight it should be based on detailed knowledge of either the structure of the membrane or the variation in β-conformation with drying in some pertinent lipid-protein model.

Maddy and Malcolm remark that many workers seem to have overlooked the possibility that cholesterol molecules may form hydrogen bonds with one another and dissolve in the hydrocarbon chains of the lipid phase; references are desirable to some of the treatments of membrane structure in which this possibility was not overlooked. The presence of proteins in extended conformations in biological membranes, far from being an "intractable element" relative to micellar transformations of the lipid phase, as Maddy and Malcolm assert, is an essential element of the only detailed theoretical treatment of such membrane transformations (*2*).

If the relevance of the highly indirect experimental approach of Maddy and Malcolm could be demonstrated first in some model system, say by elucidating the structure of the simple aqueous gelatin gel from structural studies of dried gelatin films, one might have a precedent for drawing conclusions regarding the structure of biological membranes in vivo from structural studies of dried membranes.

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3 January 1966

It should be clear from our paper that we do not exclude extended conformations, only the β-conformation, as an important structural feature of cell-membrane proteins. The term β-conformation refers to structures with extended or nearly extended polypeptide chains, each with a twofold screw axis and peptide hydrogen bonds between the chains (for example see *1*). The presence of this structure in silk and β-keratin, or in other proteins as a result of thermal or other denaturation processes, leads to a cross-linked structure insoluble in water; there has been no previous suggestion that it needed additional stabilizing forces. We showed that the proteins of the erythrocyte ghost are not exceptional in this respect, in that the β-form can be observed in dry denatured films. As to Kavanau's proposed stabilization by hydrophobic interactions, it is difficult to see how these occur between protein and lipid. Haydon and Taylor have pointed out the steric problems (*2*); if the protein were in the β-form these would be particularly severe, since the nonpolar side chains would not be long enough to penetrate beyond the polar lipid head-groups. This is a fundamental probem that Kavanau does not answer in his detailed theoretical treatment.

During further work we have obtained infrared spectra of fresh erythrocyte ghosts suspended in D_2O and of a solution of ghost protein in D_2O; both spectra show an amide I band which is symmetrical about 1648 cm^{-1} and which is unaffected by drying. Thermal denaturation, followed by drying of the protein, leads to a broader asymmetrical band with peaks at 1648 and 1632 cm^{-1}. We attribute the latter peak to formation of denatured β-protein: this peak is not detected in the unheated preparations.

These observations support our conclusion that there is no experimental foundation for the supposition of an extensive array of protein in the β-conformation adjacent to the lipid; they meet Kavanau's criticisms more directly than would experiments on gelatin. Since gelatin, with its high proline content, does not form the β-conformation it is difficult to see how it could settle the point at issue.

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