value taken. The migrations are not free movements into a liquid phase. If a clot is present, the cells move along the fibrin micellae. But if no clot is present, the cells will migrate along the walls of the capillaries, and the results are very similar.

For the experiments, it was most convenient to make a single measurement after 16 hr. However, as shown in Fig. 2, rate studies indicate that when the migration distance between two subjects varies, this is a result of the difference in the rate of migration during the early hours of the experiment.

The normal subjects used for these experiments were laboratory personnel. At the time of the experiment each subject was asymptomatic. It was discovered that symptoms from slight infections were accompanied by a marked effect on the leucocyte migration.

TABLE 1

AVERAGE MIGRATION DISTANCE OF LEUCOCYTES FROM NORMAL SUBJECTS

Subject	Sex	Blood type	No. expt	Mean (mm)	Standard deviation (mm)
KE	F	A, Rh +	5	0.47	0.05
JH	F	A, Rh +	6	0.56	0.04
MK	M	A, Rh +	18	0.71	0.10
JL	M	A, Rh +	13	2.16	0.38
EAS	F	O, Rh +	5	2.47	0.61
CBF	M	O, Rh +	5	2.64	0.26

Table 1 records the data on experiments designed to evaluate the technique. The cells of normal persons were here suspended in the individual's own plasma. Though the cell migration of a given individual was relatively constant on different days, it is clear that a great deal of variation exists between individuals.

TABLE 2

AVERAGE MIGRATION DISTANCE OF LEUCOCYTES IN AUTOLOGOUS AND HOMOLOGOUS PLASMA

Plasma	MK cells (mm)	JL cells (mm)
MK	0.54	0.78
JL	1.63	1.93

Table 2 summarizes the results of six experiments designed to ascertain the importance of cells and plasma in the migration of the leucocytes. Two normal males having widely different average migrations were chosen. Both had type A, Rh positive blood. The migration of the cells of each individual was measured both in his own plasma and in the plasma of the other individual. MK cells in MK plasma migrated an average distance of 0.54 mm, and JL cells in JL plasma migrated an average distance of 1.93 mm. However, when MK cells were tested in JL plasma, their migration increased to 1.63 mm, and when JL cells were tested in MK plasma, their migration decreased to 0.78 mm. While there is still a difference in the migratory ability of the cells of the two subjects, it is evident that the plasma dictates to a large degree the rate of cell migration.

Similar experiments were repeated on types A, O, and B individuals. The results were consistent with the findings on the two initial subjects. In another series of experiments, the blood groups were mixed. Under such circumstances, if migration was not prevented by agglutination of the erythrocytes during the preparation of capillary tubes, the results were also consistent with those shown in Table 2.

The substance or substances contained in the plasma which condition the migration of leucocytes are heatlabile and nondialyzable. At present we are attempting to characterize the substances further by fractionation of the plasma proteins according to the small volume cold alcohol technique (*2*). Preliminary data indicate that when Fraction 3 of a slow plasma is added to a fast plasma, the migration of leucocytes in that plasma is markedly suppressed. And, when Fraction 2 of a fast plasma is added to a slow plasma, the migration of leucocytes in that plasma is increased.

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Manuscript received January 19, 1953.

Hepatic Tumors Due to Prolonged Ethionine Feeding[1]

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Ethionine (α-amino-γ-ethylthiobutyric acid) is an analogue of methionine and one of its biologic antagonists (*1, 2*). It produces, within a few days, fatty metamorphosis of the liver in female but not in male rats (*3, 4*). The lesion was considered the result of interference with amino acid or protein metabolism (*5*). Feeding synthetic diets containing 0.5% ethionine to male and female rats for 4 weeks produces a reduction of the fat content and severe liver cell damage (preceded by diffuse fatty metamorphosis and central necrosis). The liver shows diffuse infiltration by inflammatory cells as well as intralobular fibrosis and bile duct proliferation (*6*). Large liver cells with huge, sometimes multiple, nuclei and very large eosinophilic nucleoli are noted as well as irregularity in the appearance of the bile ducts (*7*). These pictures, interpreted as irregular regeneration, raised the question whether tumor formation may eventually result

[1] Supported by a grant from the Jerome D. Solomon Memorial Research Foundation.

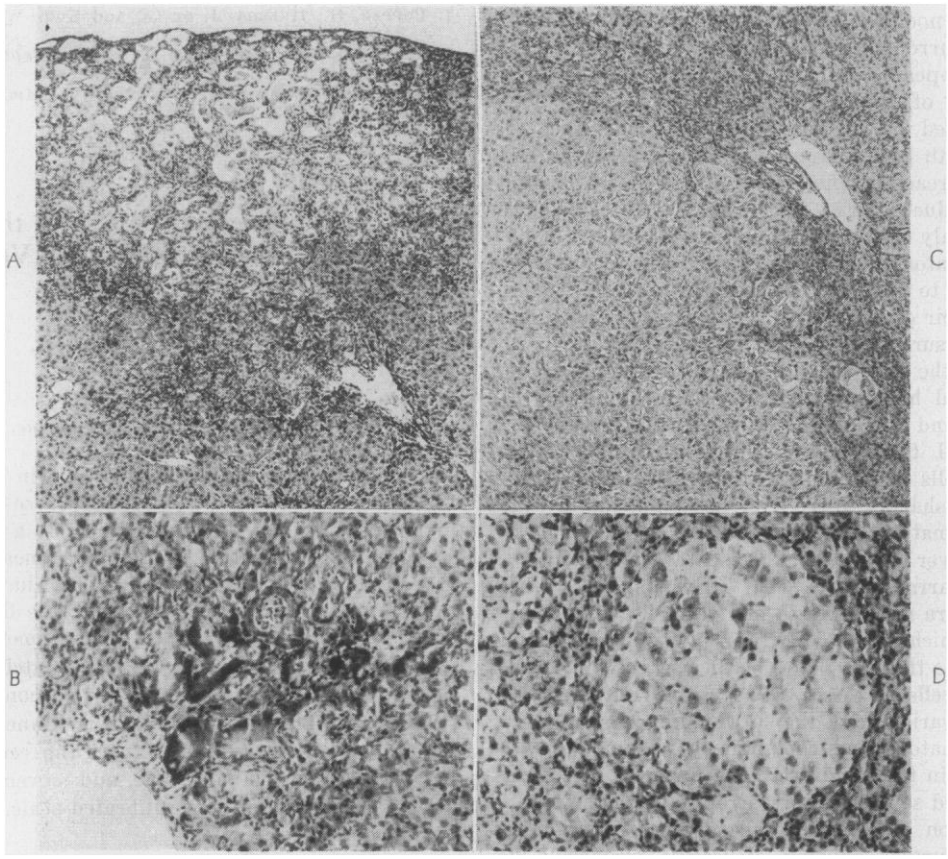

FIG. 1.

Photomicrographs of rat liver. *Upper left,* 0.2% ethinoine diet for 104 days. Subcapsular nodule consisting of proliferated bile ducts with dilated lumen containing mucinous material. The irregularly demarcated nodule connects with a portal triad (50 ×). *Lower left,* 0.5% ethionine diet for 51 days. Circumscribed heightening of bile duct epithelium with piling up of the cells and hyperchromasia of their cytoplasm and nuclei. Between the cells and in the lumen segmented leukocytes are found (112 ×). *Upper right,* 0.5% ethionine diet for 51 days. Fairly sharply demarcated nodule consisting of liver cells varying in character from the surrounding tissue in which the liver cells are irregularly arranged and dense inflammatory infiltration is noted (40 ×). *Lower right,* 0.5% ethionine diet for 51 days. Small nodule consisting of large liver cells forming several cell thick plates and revealing large nuclei and nucleoli and loose eosinophil cytoplasm (250 ×).

from this diet. Therefore, the attempt was made to keep rats (females) on these diets for longer periods.

The survival time varies markedly in different groups of rats on the 0.5% ethionine diet although most die within 5 weeks. Some groups, however, lived more than 50 days. Other groups of rats which became sick after 4 weeks were placed on a stock diet for 10 days, to be returned subsequently to the 0.5% ethionine diet. Finally, rats were kept for prolonged periods on diets containing 0.2% ethionine. All ethionine diets consisted of 16% casein, 75% sucrose, 5% corn oil with the addition of essential salts and vitamins; the riboflavin content was relatively low, being 0.42 mg/100 g. The diets had an approximate methionine content of 0.4%. Control rats on the synthetic diet without ethionine showed no changes.

Nodules consisting of either liver cells (hepatomas) or bile ducts (cholangiofibrosis or cholangiomas) were seen in 8 of 12 rats on the 0.5% ethionine diet for 51 days, in 1 rat on the 0.5% ethionine diet for 77 days, in 2 of 4 rats on the 0.2% ethionine diet from 87 to 104 days, and in 2 of 6 rats which had been kept on alternating 0.5% ethionine and stock diets between 60 and 67 days. Such lesions were not found in rats which had been on 0.2 or 0.5% ethionine diets for shorter periods.

The cholangiofibrotic or cholangiomatous nodules were usually multiple. They were up to 1½ mm in diameter and connected with portal triads (Fig. 1A). Some were subcapsular. Their epithelial cells were high cuboidal, densely arranged, and sometimes piled up. The basal nuclei were dark. The intensely basophilic cytoplasm occasionally contained vacuoles giving PAS (periodic acid-Schiff) reaction. The ductal lumen was dilated, occasionally cystic, and filled with a dense material also giving PAS reaction indicating a mucinous character. Segmented leukocytes were often found between the cells and in the ductal lumen. The basement membranes were thickened and dense collagenous and reticulum fibers surrounded the ducts

within the nodules. The demarcation of these nodules from the surrounding liver tissue was not sharp. Early changes appeared near the portal triads. They were alterations of the proliferating smallest bile ducts, characterized by heightening of the bile duct epithelium with hyperchromasia, piling up of the cells, and PAS reaction (not given otherwise by proliferating bile ducts) (Fig. 1B). This change occasionally involved only one segment of the wall of the bile duct.

The hepatomas, also usually multiple, consisted of nodules up to 2 mm in diameter which, on the greatest part of their circumference, were sharply demarcated from the surrounding liver tissue (Fig. 1C). The nuclei of the cells were, as a rule, large, vesicular, and showed huge nucleoli. The abundant cytoplasm was loose and eosinophilic. The cells were arranged in several cell thick plates with few capillaries and Kupffer cells between them (Fig. 1D). The nodules contrasted sharply to the liver tissue outside in which the inflammatory and fibrotic changes were marked and the liver cells had a denser cytoplasm and an irregular arrangement. The early stages of these nodules were small groups of liver cells (5 to 8 in a section) which represented focal multiplication of the liver cells so that the plates became several cells thick. The liver cells in these small groups resembled each other but varied from the surrounding tissue.

Hepatomatous and cholangiomatous nodules were found within the same liver. The pancreas of the animals showed severe fibrosis, atrophy of the acini, and vacuolization of the islet cells. These lesions represented a further advance of lesions previously described (*6, 8, 9*).

It appears, thus, that feeding diets containing an amino acid antagonist produces, in relatively short time and rather consistently, small multiple hepatic tumors composed of either liver cells or bile ducts varying in character from those in the surrounding tissue. The precursor stages of the nodule formation can be prevented or corrected by methionine administration. Although abnormal growth and anaplasia are seen histologically, it cannot be determined that the tumors represent malignant growths. No agreement is found in the literature as to whether the lesion called cholangiofibrosis or cholangioma represents neoplasia at all; this is reflected in the variety of names chosen for this lesion which is characteristically produced by carcinogenic dyes. It also cannot be ascertained whether the tumor formation is caused by ethionine directly or results from the excessive regeneration due to persisting injury to liver cells and bile ducts associated with diffuse fibrosis.

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Manuscript received January 12, 1953.

Compact Flowmeters for Use in the Unanesthetized Animal, an Electronic Version of Chauveau's Hemodrometer[1]

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Certain characteristics are desirable in a flowmeter for use in animal experimentation. These include (1) high sensitivity, (2) low resistance, (3) a regular and reproducible calibration, preferably linear, and (4) ease of use. Attempts to achieve these have extended over more than a century. Probably the first successful instrument was Chauveau's hemodrometer (*1*). The essential feature was hit upon while watching needles thrust into arteries. His first device consisted of a straight cannula with a rubber membrane as part of the wall. A lever extended from the center of the stream through this membrane, and movements of the lever were read against a calibrated scale. On a later

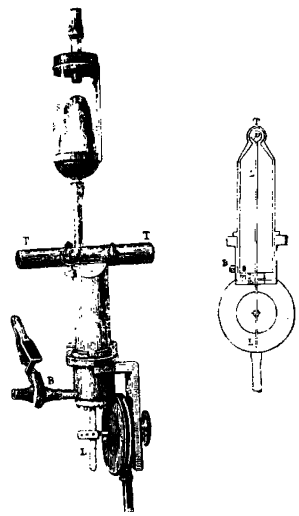

FIG. 1. Chauveau's hemodrometer as diagrammed by Luciani (*5*). The figure on the left shows the entire instrument, the cross section on the right is of the inverted, lower portion of the instrument. S, a sphygmoscope used to record the blood pressure; TT, a tube used to cannulate; L, a lever suspended by a rubber membrane at m. The lower end of the lever within the stream carries a paddlelike obstruction, while the outer end moves a tambour connected by tubing to a recording tambour.

[1] Aided by grants from the State of Washington Research Fund for Biology and Medicine and the National Heart Institute, USPHS.