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Alcohol, Sludge, and Hypoxic Areas of Nervous System, Liver and Heart[1]

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In 30 adult humans (13 females, 17 males) microscopic observations were made of blood flow and the conditions of the small vessels in the conjunctiva, and at the same time a blood sample was taken for determination of blood ethyl alcohol concentration. Ethanol concentrations ranged from zero to 328 mg/100 ml. With increasing concentrations of alcohol in the blood, the size of aggregated or agglutinated blood cell masses increased, and the forward rates of flow in small vessels decreased correspondingly.

With the higher concentrations of blood alcohol and the more severe reduction in forward flow rates, the numbers of vessels in stasis, plugged, occluded, and with no flow increased significantly. Within the extreme upper concentrations of ethanol (225 and 328 mg/100 ml blood) some small vessels were ruptured, producing microscopic hemorrhages into the contiguous bulbar conjunctival tissue.

No arrangement of the data, other than in ascending order of blood alcohol concentrations, has given any thus far recognizable trend of meaning.

Mechanisms are described whereby reduced rates of blood flow through capillaries and the plugging of capillaries damage brain, liver, and heart.

This paper presents data on 30 intoxicated human subjects, correlating concentrations of ethyl alcohol in drawn blood samples with microscopically observed degrees of *in vivo* intravascular agglutination of blood cells (sludged blood), degrees of reduction of flow rates through small vessels, stasis (one form of pathologic plugging of vessels (Krogh 1929)) and microscopic hemorrhages. Comparison with previously established knowledge indicates that alcohol sludge forcibly reduces the rates of supply of oxygen molecules to nerve cells, to cells of the central zones of the liver lobule, and to certain anatomically defined small volumes of cardiac muscle.

In healthy normal human beings blood cells are not agglutinated (reviewed by Knisely, 1965a).

Intravascular agglutination of the blood after the ingestion of alcohol has been reported repeatedly. Hueter (1874) appears to have been first. Knisely *et al.* (1947) listed five cases of sludge in automobile accident victims in traumatic shock complicated by hemorrhage and alcoholism. Bellis and Snow (1950) reported the presence of sludge in alcoholics. Hirschboeck and Woo (1950) listed four cases of acute alcoholism in which sludge was present. Arajarvi and Wallgren (1954) observed the development of a sludge in bulbar conjunctival vessels after the exposure of the conjunctiva to alcohol vapor. Forsander and Suomalainen (1955), in a controlled experimental study, reported

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that sludge was produced by drinking brandy and soda. In their five human subjects, blood alcohol levels from 0.45 to 1.55 per m.l (45–155 mg/100 ml blood) were accompanied by a sludge that persisted after the alcohol concentration in the blood had begun to fall. Bloch (1956) listed 35 cases of acute alcoholism in which a sludge was present. Shideler (1960) correlated decreased electrophoretic mobility of erythrocytes with the intravascular agglutination produced in rabbits by ethyl alcohol. However, we have found no studies in which concentrations of alcohol in samples of the subject's blood were correlated with the degree of sludge produced in the subject or with the consequences of that sludge.

MATERIALS AND METHODS

Thirty-six subjects were studied. All were private patients in a moderately expensive sanitorium. (They were not derelicts; none presented clinical evidence of disease or pathology other than the effects of alcohol.) For various reasons the data on six were discarded. In one, a moderate degree of intravascular agglutination was observed and to our surprise the laboratory reported zero alcohol in his blood sample. A subsequent check showed that the microscopic study of the subject's circulating blood took place immediately upon his admission to the hospital, and that through some misunderstanding the blood sample was not drawn until 48 hours later.[2] Not only was the data in this case discarded, but the experience led us to draw the relevant blood sample routinely at the time of microscopy.

Microscopic observations were carried out in each case on the bulbar conjunctiva and underlying scleral vessels (Knisely *et al.*, 1947; Knisely, 1965a) using a portable, hand-held monobjective monocular microscope (Knisely, 1960). This instrument, constructed in our own research instrument shop,[3] gives good resolution at 24×, 48×, and 64×. It is no more difficult to use than an ophthalmoscope. Low magnifications were selected intentionally; if masses of aggregated or agglutinated blood cells and clear plasma spaces between them are large enough to be visible at low magnifications, then the subject certainly has significantly agglutinated blood. At these magnifications, rates of blood flow and evidence of leaking, sacculations of vessels, stasis, impactions, and small hemorrhages can also be detected. Blood alcohol determinations were made by the method of Aull and McCord (1964).

Permission to study each subject was obtained from the patient's physician and from the patient himself or from members of his family. During a 17-month period all patients admitted to the hospital for intoxication were studied.

The patient's chart recorded significant microscopic observations and other pertinent information, his serial number, age, sex, drinking history, amount of liquor claimed to have been consumed in the past 24 hours, whether the patient had been bumped or bruised by falling or fighting, drugs with which the patient was currently being treated, and blood cell counts (red and white), hemoglobin, and volume of packed

[2] A separate, unpublished study has shown that sludge induced by alcohol can persist for several days after the drinking has stopped.

[3] It is a privilege to thank Mr. Emil Matt, chief of our research instrument shop, for making this microscope.

cells, the concentration of alcohol found in the patient's blood, and the microscopically observed physical condition of his blood, blood flow, stasis, plugging impactions, and visible microhemorrhages.

The data on bumped and bruised patients and those with recognizable disease were discarded because these could be expected to contribute to or alter the severity of intravascular agglutination found (Knisely *et al.*, 1945; Knisely, 1965b).

It soon became apparent that neither the statements of the patients, nor those of his friends or relatives, concerning the amount of alcoholic beverages (usually claimed to be whiskey) consumed within the 24 hours previous to admission had any relevance to the concentration of the ethanol found in his blood. Most of the patients had long histories of being reasonably competent people who periodically "went on a bender." They were periodic obsessive drinkers who came or were brought to the hospital when well into the drinking episode. It was impossible to establish either how long the current bout had lasted, or whether at the time of hospitalization the consumption of alcohol was increasing or tapering off.

RESULTS

The data on the 30 relevant subjects are arranged in the order of increasing concentrations of ethanol found in the blood, and paired with the microscopic observations of blood, blood flow, plugging (i.e., occlusion of vessels by stasis), and visible hemorrhages (Table 1). Table 1 shows:

1. Patients with increasing concentrations of ethanol in the blood showed a comparable increase in the degree of aggregation or agglutination of the microscopically observed bloods.

2. Severe intravascular agglutination is associated with a drastic reduction of blood flow rates through small vessels.

3. In this series, no stasis (i.e., occlusion of observed vessels) was observed when blood ethanol concentrations were less than 210 mg/100 ml of blood.

4. At 200 mg ethanol/100 ml of blood, agglutination, "slow flow," darkened venous blood, engorgement, and wall sacculation were moderate; a condition of "pre-stasis" existed.

5. Between concentrations of 215 and 236 mg ethanol/100 ml blood, only one subject had vessels in stasis.

6. Those subjects with 255–328 mg ethanol/100 ml of blood all had a heavy or severe sludge, blood flowing slowly or very slowly, and significant numbers or percentages of visible small vessels in stasis, i.e., plugged or occluded, with no blood flow through them.

7. No subject with less than 255 mg ethanol/100 ml blood had visible small hemorrhages into his bulbar conjunctiva. Two subjects with 255 mg ethanol did not have hemorrhages, and one patient at this concentration had hemorrhages.

8. One subject at 255 and another at 281 mg ethanol/100 ml blood had very severe sludge, slow flow in one case, and very slow flow in another, the blood being a dark venous color; in both subjects, microscopically easily visible definite hemorrhages were present in the bulbar conjunctiva. (The subjects had no record of being bumped or injured in any way that could have initiated these hemorrhages.)

Although all the subjects in this series were admittted to the hospital because at the time of admission they were said to be intoxicated, it is obvious that those having the lower blood alcohol levels were not intoxicated at the time the blood was drawn and the blood and vessels in their bulbar conjunctiva observed. None of the subjects in this series had blood levels in excess of 328 mg ethanol/100 ml.

Obviously, many more observations of patients in acute alcoholism are needed. Also, studies of this kind need to be extended to include patients having blood alcohol concentrations from approximately 250 mg ethanol/ml blood up to and through concentrations that are known to be lethal, that is, in the range of 450–800 mg/ml blood (Bogen, 1927; Turner, 1932).

The current data may be summarized as follows: with increasing concentrations of alcohol in the blood, an increase in the sizes of the blood cell masses is correlated with a progressive reduction in the forward flow rates through small vessels. With the higher concentrations of blood alcohol and the more severe reduction in forward flow rates, there was an increase in the numbers of vessels in stasis, with no flow through them. Within the extreme upper concentrations of ethanol encountered in the study at 255 and 328 mg/100 ml, not only were numerous small vessels in stasis, but some, we may deduce, had ruptured, giving microscopic hemorrhages into the contiguous bulbar conjunctival tissue.

DISCUSSION

To derive meaning from the above observations, accessory information is necessary. Microscopic observations of conjunctival vessels of healthy young men show that as they ingest alcohol, their blood cells begin to agglutinate, and with the consumption of increasing amounts of alcohol, a severe agglutination develops (unpublished results). This agglutination is a direct consequence of alcohol in the blood. The agglutination persists for variable periods of time. When large amounts of alcohol are ingested, some degree of agglutination persists for several days.

Pennington has shown that in living rabbits given alcohol the blood is agglutinated in every tissue and internal organ that could be transilluminated for microscopic study (unpublished observations). In the case of a man who drank himself to death by ingesting more than a quart of whiskey in less than 3 hours, at autopsy agglutinated blood was present in the vessels of all internal organs observed. When agglutinated blood is seen in the conjunctival vessels of intoxicated subjects, it is almost certain that agglutinated blood is present throughout the entire vascular system.

Mechanisms whereby the ingestion of ethyl alcohol damages the tissues of the drinker have been largely speculative. These observations demonstrate a major mechanism of tissue damage, namely, severe local hypoxias or anoxias which, in the chronic alcoholic, are repeated at longer or shorter intervals over and over again, *ad infinitum*.

The following concepts are commonly held:

1. Extensive pathology is found in the nervous system of the acute and chronic alcoholic.

(*a*) At gross autopsy, the brain of the alcoholic is often edematous, the so-called "wet brain" (Courville, 1966). Frequently it contains many congested small vessels, areas of atrophy of the cerebral convolutions, and multiple small or large hemorrhages from small vessels into the substance of the brain itself.

TABLE 1

	Patient[a] No., sex, age	Mg alcohol/ 100 ml blood	Degree blood agglutination[b]	Numerical coding of agglutination	Sub-totals[c]	Degree of reduction of rates of blood flow	Coding of reduced flow[d]	Sub-totals[e]	Occlusion of vessels by stasis[f]	Coding of stasis	Sub-totals[g]	Comments on observed occlusion by stasis	Hemorrhages into conjunctiva
1.	(24 F 38)	0.0	N	0		N	0		N	0		No stasis.	
2.	(29 M 41)	12	LMin	1		N	0		N	0		No stasis.	
3.	(30 M 51)	49	Min	2		SF	2		N	0		No stasis,	
4.	(20 F 41)	75	Min	2		N	0		N	0		No stasis.	
5.	(27 F 59)	112	Min	2	T = 7	N	0	T = 2	N	0	T = 0	No stasis.	
6.	(32 M 51)	137	Mo	4		Fd	1		N	0		No stasis.	
7.	(30 M 58)	156	H	5		SF	2		N	0		No stasis.	
8.	(14 F 41)	165	Mo	4		N	0		N	0		No stasis.	
9.	(3 F 40)	165	Mo	4		Fd	1		N	0		No stasis.	
10.	(5 M 68)	185	Mil	3	T = 20	Fd	1	T = 5	N	0	T = 0	No stasis.	
11.	(8 F 55)	185	Mo	4		Fd	1		N	0		No stasis.	
12.	(26 M 39)	185	Mo	4		Fd	1		N	0		No stasis.	
13.	(9 M 39)	185	Mo	4		Fd	1		N	0		No stasis.	
14.	(21 F 58)	200	Mo	4		SF	2		P	1		Blood dark, vessels engorged, sacculated, pre-stasis.	
15.	(2 M 56)	210	H	5	T = 21	SF	2	T = 7	S	2	T = 3	Very little flow in any vessel; one large venule occluded, in stasis.	
16.	(1 F 42)	215	Mo	4		SF	2		N	0		Blood dark.	
17.	(13 M 56)	225	Mo	4		SF	2		N	0			
18.	(11 M 65)	225	Mi	2		SF	2		N	0			
19.	(15 F 55)	235	H	5		VSF	3		S	2		Some small vessels occluded, in stasis.	
20.	(19 M 65)	236	H	5	T = 20	SF	2	T = 11	N	0	T = 2		
21.	(6 F 48)	245	Mo	4		SF	2		N	0			
22.	(28 F 38)	251	H	5		VSF	3		N	0			
23.	(4 M 60)	255	VH	6		SF	2		S	2		Blood dark; many vessels occluded, in stasis.	
24.	(7 M 50)	255	H	5		SF	2		S	2		One large venule occluded, in stasis.	
25.	(17 M 52)	255	H	5	T = 25	SF	2	T = 11	S	2	T = 6	Blood dark. 50% of vessels in stasis.	Some hemorrhages present.

26. (10 F 56)	265	H	5		VSF	3		N	0		
27. (22 M 31)	265	H	5		SF	2		P	1	Vessels engorged, sacculated, pre-stasis.	
28. (23 M 60)	265	H	5		SF	2		S	2	Numerous large vessels occluded, in stasis.	
29. (25 M 51)	281	H	5		VSF	3		S	2	Blood dark, many vessels occluded, in stasis.	Microhemorrhages present.
30. (31 F 43)	328	H	5	T = 25	SF	2	T = 12	S	2	T = 5 Many small vessels occluded, in stasis.	

[a] Patients in the order of increasing concentrations of alcohol in the blood.

[b] N, Normal, 0; LMin, Low Minimal, 1; Min, Minimal, 2; Mil, Mild, 3; Mo, Moderate, 4; H, Heavy, 5; VH, Very Heavy, 6.

[c] T, in each case, is calculated by adding the five items above the T in the column Numerical Coding of Agglutination. Notice that although the items of numerical coding increase by small increments, the sums of groups of five (i.e., the T's) increase quite significantly.

[d] N, Normal, 0; Fd, Flow decreased,1; SF, Slow Flow, 2; VSF, Very Slow Flow, 3.

[e] Each of the T's is a subtotal arrived at by adding five items in the column entitled Coding of Reduced Flow. Notice that although there are small variations in the items of coding of reduced flow, the sums of groups of five steadily increase.

[f] In the column Occlusion of Vessels by Stasis, N = no stasis, P = prestasis, and S = stasis. Note that with increasing concentrations of alcohol in the blood, the symbol S occurs with increasing frequency.

[g] In each case T, the subtotal, is the sum of the preceding five items in the column to the left.

(*b*) Chronic ingestion of alcoholic beverages in sufficient amounts over sufficient periods of time damages some, and results in the death of other nerve cell bodies and fibers (Courville, 1966; Lynch, 1960; Victor and Adams, 1962). Peripheral nerves often show extensive morphologic alterations and degenerations (see Courville's scholarly monograph, 1966).[4]

2. Damage to the liver, fatty or cirrhotic, is not uncommon (Rubin and Lieber, 1968).

3. At autopsy, the heart of the alcoholic is often flabby and shows histopathologic damage to localized areas of the muscular walls of the heart, including at times papillary muscles (Hibbs *et al.*, 1965; Pintar *et al.*, 1965; Heggtveit, 1965; Ferrans *et al.*, 1965a, 1965b).

4. The chronic alcoholic is particularly susceptible to infection (Pickrell, 1938; Conn, 1964; Tisdale and Klatskin, 1960).

5. Neurons are extremely sensitive to hypoxia and anoxia. Fundamental to the conclusions and working hypotheses to be developed is the concept that with severe, prolonged hypoxia or anoxia destruction of nerve cells occurs.

6. There is no evidence that oxygen is stored anywhere in the body. The only "storehouse" of oxygen is the blood in the pulmonary veins, which in turn feed blood into the arterial system to be distributed to the various organs and tissues.

7. Destroyed nerve cells are not replaced.

8. When the oxygen supply to a nerve cell is decreased for a sufficient length of time (two variables), the cell may stop functioning (from which it may recover). When severe hypoxia continues, the nerve cell dies, autolyzes, and is then removed from the nervous system (Courville, 1953).

9. When the oxygen supply is cut off completely, nerve cells are known to be irreversibly damaged in from 3 to 10 or 20 minutes (Gildea and Cobb, 1930; E. Krogh, 1945).

Items *5* and *9* emphasize the importance of maintaining an uninterrupted and adequate rate of supply of oxygen (molecules per unit time) to *each* and *every* nerve cell *continuously*.

10. Oxygen is supplied to nerve cells only by way of the vascular system and capillaries.

Reneau *et al.* (1967) developed a mathematical simulation of oxygen release, diffusion, and consumption in the capillaries and tissues of the human brain. Equations developed and programmed for computers described the mechanisms by which molecular oxygen is transported from red cells (while the red cells are carried in blood flowing longitudinally through capillaries), into moving plasma, and then radially out to and through the capillary wall into the surrounding tissues. Such equations make it possible to solve a number of problems. For instance, what are the specific effects

[4] Courville, in his comprehensive, scholarly monograph, "Effect of Alcohol on the Nervous System of Man" (1966), has chapters entitled: "Cellular changes in the brain in acute alcoholic intoxication and delirium tremens"; "Hemorrhagic encephalopathy ('Encephalitis hemorrhagica superior' of Wernicke)"; "Peripheral neuropathy"; "Alcoholic atrophy of the cerebral cortex"; "Pathology of the chronic alcoholic psychoses (Korsakof's Psychosis; alcoholic pellagra; chronic alcoholic deterioration)"; "Postalcoholic commissural and central necrosis (Marchiafava-Bignami Disease)"; "Alcoholic cerebellar degeneration"; and "Regressive changes in the spinal cord incident to chronic alcoholism (intrafunicular degeneration; posterolateral sclerosis)."

of forcibly reducing the linear rates of flow of blood through capillaries, on nerve cells along the lengths of, and at various positions between, capillaries?

The mathematical model predicts that as a consequence of reduced forward rates of flow through capillaries, a minute, finite volume of tissue equidistant between two neighboring capillaries, and near the venous ends of the capillaries, becomes hypoxic. With progressively decreased rates of flow, these volumes increase in size. As these hypoxic volumes enlarge, they include the capillary endothelium (see Figs. 1 and 2).

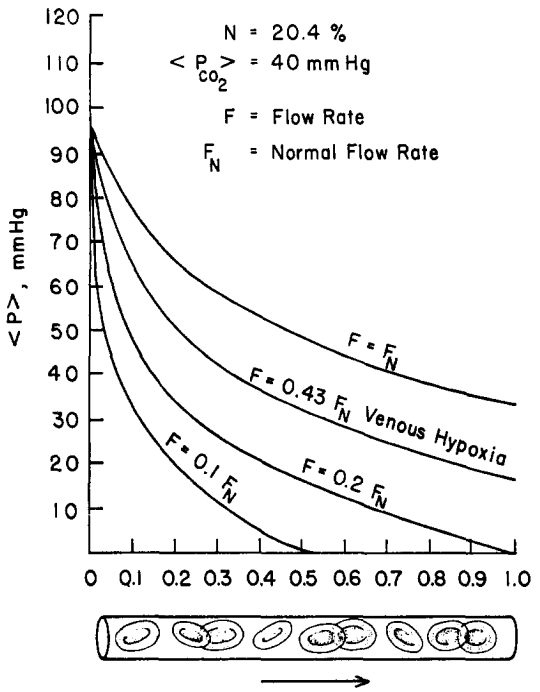

FIG. 1. Axial partial pressure profiles in the capillary for reduced flow rates. All other conditions are normal. $N = 20.4\%$ = the oxygen capacity of blood (20.4 ml O_2/100 ml of arterial blood). $\langle P \rangle$ = the space average partial pressure of oxygen during steady flow (averaged across the cross-sectional area of the capillary). $\langle PCO_2 \rangle = 40$ mm Hg (shows which oxygen dissociation curve was used in the calculations). The numbers along the abscissa are fractions of total capillary length.

Since oxygen is consumed by a zero-order reaction and an infinite number of "oxygen sinks"[5] exist, enormous numbers of such anoxic anatomical units of tissue develop (see experiments of Davis and Bronk, 1957). Theoretically, a loss of consciousness should develop when the flow rate of blood through brain capillaries is reduced to 46% below the normal value (Optiz and Schneider, 1950).

It should be noted that vessels need not be plugged to produce local areas of anoxia. Anoxic areas develop even while blood is moving. Obviously a "zero" rate of flow in plugged vessels also produces anoxic tissue areas (Cohnheim, 1872; Scharrer, 1944).

[5] An oxygen "sink" is a small unit of space to which oxygen goes by diffusion and at which it unites with something and thus stops moving by diffusion. A whole tissue cell may be considered an oxygen sink, or a point on a mitochondrium which accepts oxygen is an oxygen sink.

Anoxia for a sufficient length of time causes the endothelium to weaken, dilate, "sacculate," and to lose its ability to retain blood plasma proteins, and thereby initiates edema of the surrounding tissue (Zweifach, 1940; Starr, 1926; Starling, 1926; Landis, 1928; Maurer, 1940, 1941a, 1941b; Warren and Drinker, 1942; Drinker, 1942). The loss of fluid containing dissolved plasma proteins from small vessels into tissue spaces constitutes one type of edema. Currently, the specific factors that initiate the different kinds of brain edema are under active investigation (Klatso and Seitelberger, 1967). In conditions where the anoxia is sufficiently prolonged, the endothelium may permit the escape of red cells (diapedesis) or rupture, and permit local hemorrhage (E. R. and E. L. Clark, 1935; Knisely and Lockard, 1955).

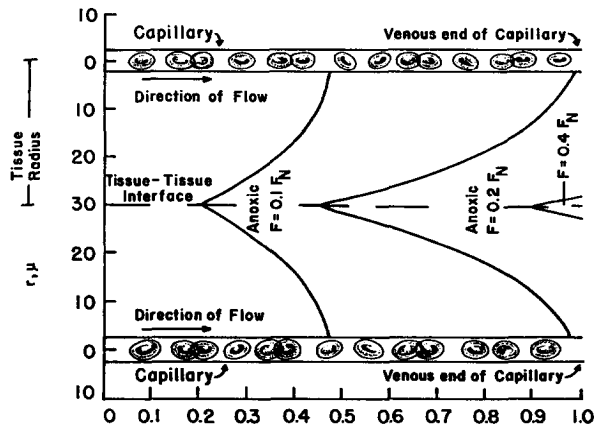

FIG. 2. Anoxic areas of tissue between parallel capillaries as a function of reduced capillary flow rates. All other conditions are normal. When the rates of forward flow are sufficiently reduced, anoxic areas develop between capillaries regardless of whether neighboring capillaries are parallel to each other or have any discernible geometric arrangement. Tissue anoxia develops irrespective of whether the flow in neighboring parallel capillaries is in the same or opposite directions. The effect will appear first in areas between parallel capillaries having flow in the same direction.

When examined at autopsy, small vessels from which all of the fluid has been lost are impacted with concentrated cellular material and are described as "congested."

Ethanol, by initiating the agglutination of the blood cells, (*1*) reduces the forward rates of flow, (*2*) initiates local, anatomically defined, minute areas of severe hypoxia or anoxia, (*3*) causes anoxia of neurons, which destroys them, and (*4*) causes leaking of endothelium, which leads to edema and ultimately diapedesis, plugging of vessels, "congestion," and hemorrhage.

Successive episodes involving removal of dead nerve cells and reparative connective tissue responses (Spielmeyer, 1922) can, in conjunction with the above types of repeated damage, produce the complex neurohistologic pictures found in different clinically defined conditions such as Korsakoff's syndrome and peripheral alcoholic neuritis (for a list, see Courville, 1953, 1966).

If the hepatic lobule is considered as a six-sided prism, portal spaces are then located at alternate corners of the lobule. Terminal hepatic arterioles and portal venules in the portal spaces supply the sinusoids. (For the connections of portal vein and hepatic

artery to sinusoids, see Knisely *et al.*, 1948, literature reviewed by Debacker, 1957, 1967, and McCuskey, 1966.) As the sinusoids pass toward the central vein, they first branch and diverge repeatedly about halfway across the lobule and then begin to converge and anastomose, their venous ends joining the central vein of the lobule.

It is reasonable to expect as in Figs. 1 and 2 that when severely agglutinated blood is passing through the sinusoids the centers of the lobules will have a reduced oxygen supply. With successive bouts of acute alcoholism it is reasonable to expect that the central areas of the lobule will be damaged. Repeated damage and attempts at repair probably are major factors causing the known histopathology of the chronic alcoholic cirrhoses.

Brown (1965) has shown that sets of capillaries of cardiac muscle come together in groups joining a very thin-walled venule. When blood is severely agglutinated, the oxygen supply to this area, similar to the region around the central vein of the liver lobule, should be significantly reduced. Repeated bouts of hypoxia may be major factors causing the pathologic conditions of the heart of the chronic alcoholic.

Substantial experimental evidence that sludge, produced by agents other than alcohol, damages kidney, heart, liver, and central nervous system is reviewed by Knisely (1965a).

In conclusion, ethanol, by initiating agglutination of the circulating blood cells, reduces the forward rates of flow through capillaries; initiates local, anatomically defined, minute areas of severe hypoxia or anoxia[6]; directly causes anoxia of neurons, which destroys them; and leads to leaking of endothelium, which yields edema and, ultimately, red cell diapedesis, plugging of vessels, "congestion," and hemorrhages. Similar, minute hypoxic or anoxic areas may be produced surrounding the central veins of liver lobules and surrounding minute cardiac venules.

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[6] Barcroft (1925), as a result of his studies in the Andes Mountains, noted that the hypoxia of high altitude (old terminology, "anoxic anoxia") produces symptoms similar to those of being drunk. The emotional instability, consisting of sudden changes of mood, from calmness to (apparently) unstimulated maudlin laughter to (apparently) unstimulated belligerence and back to maudlin laughter again occurred at high altitudes, quite similar to the behavior of a person who is drunk. Others have commented that being drunk produces symptoms simulating those of high-altitude hypoxia. Considering that the "anoxic hypoxia" of high altitude and the "stagnant hypoxia or anoxia" of acute alcoholism both forcibly reduce the rates of oxygen supply to nerve cells and capillary linings, the similarities in symptomatology are no longer surprising.

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