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Biological Action of Strongly Positive Redox Systems.

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Oxidation-reduction systems which are extremely positive from a biological point of view are continually circulating in the animal organism, but the poising effects of the redox systems of middle range such as hemoglobin are so efficient that the effects of these positive systems formed as intermediate products in the metabolism of phenyl alanine and tyrosine components of protein pass unnoticed. Only in pathological states, such as alkaptonuria, with its accompanying ochronosis, in cases of poisoning with overdosage of acetanilid, aniline, benzene, phenol, etc., can they be appreciated.

We have measured the oxidation-reduction potential of homogentisic-benzoquinone acetic acid as representative of these systems and as a substance known to circulate in the blood in alkaptonuria. This was done with bright platinum electrodes in strongly buffered solutions at fixed temperature of 25° with exclusion of air above pH 3. Table I is typical of the results. Quinone-hydroquinone was measured in the same way. Graph 1 shows the relation of pH and E_h of these systems, and for purposes of orientation hemoglobin-methemoglobin as measured by Conant[2] is included in the graph.

It has been shown by the work of Küster[1] and Conant[2] that the

TABLE I.

Oxidation of 20 mg. homogentisic acid in buffer (NaCl + HCl) with bichromate at same pH. End Point 18 cc. pH 1.984.

Oxidant cc.	Oxidant %	.03 log So/Sr	E_h Observed	E'_o Calculated	Deviation
2	5.5	.370	.5328	.5698	.0002
3	11.1	.272	.5429	.5701	.0001
4	16.7	.209	.5493	.5702	.0001
6	22.2	.163	.5544	.5700	.0000
7	27.8	.124	.5584	.5708	.0008
8	44.4	.029	.5667	.5696	.0004
9	49.9	.000	.5700	.5700	.0000
10	55.5	.029	.5733	.5703	.0003
11	61.0	.058	.5755	.5696	.0004
12	66.6	.090	.5787	.5698	.0002
14	77.7	.163	.5862	.5699	.0001
16	88.8	.270	.5971	.5701	.0001
17	94.4	.368	.6070	.5702	.0002
				Aver. .5700	

[1] Küster, W. J., *Z. Physiol. Chem.*, 1910, **66**, 244.

[2] Conant, J. B., and Fieser, L. F., *J. Biol. Chem.*, 1924, **56**, 595.

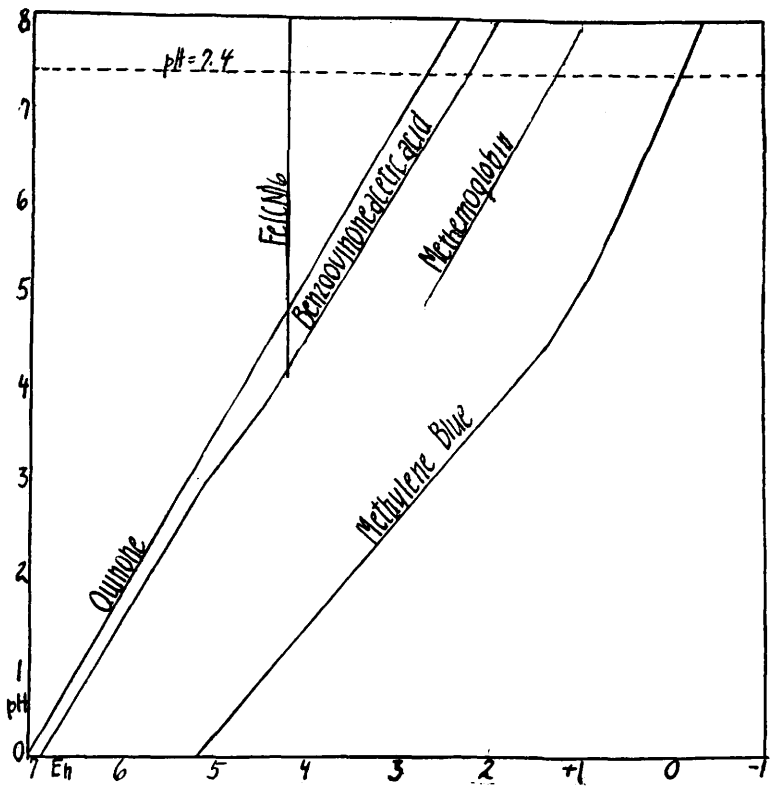

FIG. 1.

iron in methemoglobin is in the ferric state contrasted to the ferrous iron present in hemoglobin and oxyhemoglobin. The potential of the hemoglobin system is 0.15 V at body pH. Graph 1 shows that the potential of the strongly positive systems are all above 0.25 Volts at body pH. In poisoning by aromatic substances circulation of polyhydroxylated phenols causes a shift in the hemoglobin-methemoglobin equilibrium in favor of methemoglobin. This is the characteristic symptom of poisoning by these agents. The injection of acetanilid, resorcinol, etc., into dogs results in the formation of as much as 50% methemoglobin. In the clinical entity known as "enterogenous cyanosis" we have violent intestinal upsets followed by intense cyanosis in which the blood can be shown to contain methemoglobin in large quantities. This is probably due to the action of the phenol-quinone systems liberated from the damaged intestine.

Hence to the manifold functions of hemoglobin in the organism must be added its poising effect on higher oxidation systems. It

must of course be taken into account that though these systems are present in very small quantities the molecular weight of hemoglobin is 68,000 while the quinones are around 100, so that theoretically a concentration of only 20 mg. per 100 cc. of blood would be sufficient to turn the entire hemoglobin of the body into methemoglobin. The poising effect of the hemoglobin is sufficient for the normal physiological amounts formed in protein metabolism, but added amounts in aniline poisoning can and do cause the appearance of methemoglobin.

It is significant in this connection that the black pigment deposited in ochronosis is found entirely in the cartilages and sclera. These are the places where the poising effect of the hemoglobin must be absent. Hence the oxidized phase may form and this polymerizes instantly at body pH to form the melanin-like aggregates characteristic of the disease.

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Functional Heart Mechanisms.

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Studies on frogs, turtles, rabbits, cats, dogs, and man over more than 20 years and participated in by numerous associates, including Doctors Kruse, Waddel, Koenig, Criep, Hover, McLain, and Lauler have led to numerous conclusions:

I. Contraction normally begins in the superior vena cava and spreads to auricles and ventricles. The evidence and proof include: *a.* Direct observation. *b.* Simultaneous recording of contraction of veins, auricles, and ventricles alone and combined with galvanometric recording of electrical variation. (Fig. 1.) *c.* Sequence of recovery from vagus inhibition. (Fig. 2.) *d.* Transmission of premature venous contractions to auricles and ventricles. (Fig. 2.) *e.* Photographic (cinema) recording.

In man, the evidence is mainly derived from polygraphic and galvanometric records, the hitherto occasionally observed, but unexplained U-wave corresponding to the venous electrical variation observed in lower animals. It may be observed in most subjects by increasing galvanometer sensitivity as by slacking the fibre, and