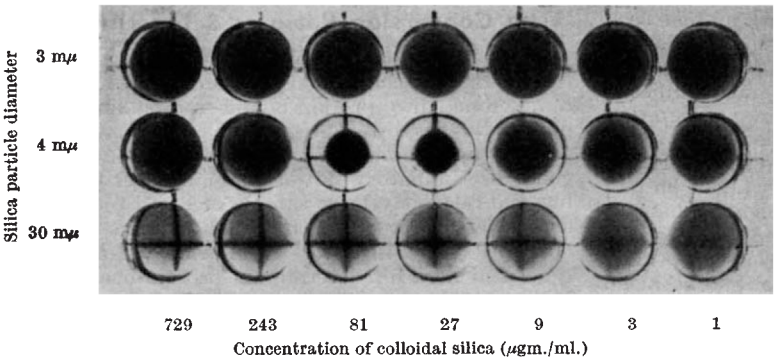

Fig. 2. Hæmagglutination plate viewed from above. 2 per cent red cell suspension was incubated with colloidal silica. Black lines were drawn on the reverse side to emphasize the transparency of the hæmolysed samples. Top row, no visible change; second row, zonal agglutination; bottom row, hæmolysis

of the colloid until it becomes negligible at about 4 mμ diameter. We have also observed that particles in the range of 3·5–7 mμ have a powerful agglutinating effect on the red cells, with a well-marked prozone (Fig. 2). Silica of 3-mμ or smaller particle size has no such activity but protects the cells against the agglutination and hæmolysis by the larger particles. This 'blocking' effect occurs only when the smaller particles are introduced into the cell suspension before the larger ones and it persists after repeated washing with saline, which probably indicates an irreversible adsorption of silica on to the erythrocyte surface. Such 'coated' red cells have other properties in addition to their resistance to the larger particles of silica. Thus they are not hæmolysed by streptolysin *O* and the saponin fragility is somewhat decreased. On the other hand, these cells become more susceptible to immune (rat) hæmolysins and to primaquine. The osmotic fragility is not altered, nor is there any obvious abnormality in appearance except that the cells do not become spherocytic when examined between glass slides and coverslips as do normal washed erythrocytes[10].

In all these experiments it is essential to use well-washed cells because even small traces of plasma markedly inhibit the action of silica. The addition of 1 : 200 plasma to the system as in Fig. 1 completely prevents hæmolysis. The plasma must, however, come in contact with silica before the latter is adsorbed by the red cells. Even a few seconds delay suffices to abolish the protective effect of the plasma. This phenomenon is evidently due to the coating of the silica by certain plasma components. The substances in question are non-dialysable and can be recovered in alkaline eluates from powdered silica which has been exposed to plasma or serum. Such eluates retain their activity after heating to 100° C.

Our observations on the agglutinating and blocking activity of silica agree with the qualitative findings of Renton and Hancock[6], who suggested that these effects may be analogous to those of agglutinating and incomplete antibodies, respectively. The present results extend this model to cover hæmolysis as well.

Although our present knowledge of the red cell structure is still fragmentary, the reaction between silica and the cell membrane may be visualized in general terms as a two-stage process: first, a rapid adsorption of the particles by the cell surface, due mainly to the ionic attraction between silica and the amino-groups at the cell surface and further reinforced by hydrogen bonds and van der Waals forces[7]; secondly, protein denaturation, the extent of which may depend purely on the geometrical relation between the colloidal particles and the protein molecules, as was previously suggested in connexion with blood clotting[5,8]. Individual silica particles of less than 3·5 mμ may not provide sufficient contiguous surface to permit significant unfolding of the much larger protein molecules. Contact with larger particles will, however, allow such unfolding (denaturation), and the resulting interference with the integrity of the cell membrane then leads to agglutination or hæmolysis according to the degree of denaturation. The geometrical picture may, of course, be oversimplified and other physical differences between the large and the small colloidal units may be contributory factors[11]. Despite these reservations, colloidal silica may prove a useful tool in the elucidation of the red cell structure.

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PHYSIOLOGY

The Psychotomimetic Properties of 3,4,5-Trimethoxyamphetamine

dl-3,4,5-Trimethoxyamphetamine (*dl*-TMA), first prepared as a homologue of mescaline in 1947[1], has remained to a large measure unexplored. A single paper has described its effects in human subjects[2], demonstrating that the drug allows stroboscope-induced hallucinations at the levels employed, namely, 0·8–2·0 mgm./kgm., orally. In the present work, *dl*-3,4,5-trimethoxyamphetamine was synthesized by the general method of Ramirez and Burger[3] and was chemically identical to that previously described[1]. Pharmacological similarity was demonstrated by the administration of between 1·6 and 2·0 mgm./kgm. as the hydrochloride, to three adult male subjects. The responses were found to be parallel in intensity and duration to those described earlier[2], although the vivid hallucinations reported were not observed.

It has been found, however, that with an increased dosage of the drug, the psychotropic response changed in a most dramatic manner. Dosages of 2·8–3·5 mgm./kgm. were given to five adult male subjects, all of whom had had previous experience with either mescaline or lysergic acid diethylamide.

The physical changes observed were similar for all subjects employed. In each case, after about half an hour, there ensued a period of autonomic distress, characterized by sweating, tremor, and chills as well as nausea and dizziness. This phase lasted no more than an hour. The slight but definite systolic blood pressure increase of about 10 mm. mercury returned to normal at the end of this phase. The concurrent diastolic increase was barely perceptible (*c.* 2 mm. mercury). During the remainder of each experiment (approximately another 6–8 hr., which includes the period of extreme mental derangement described below) very few overt physical signs of drug effect were evident. Pupillary dilatation and slight motor inco-ordination were noted. Pulse increase was negligible.

The psychic changes observed, however, were extreme and showed considerable individual variability. The initial effects, at about 2 hr. from the ingestion of the drug, were mescaline-like, involving intensification of visual experience, including amplification and distortion of colour, texture, form, and spatial relationships. These effects were distinctly less than those expected from a pharmacologically equivalent dose (2×) of mescaline. Auditory and tactile sensations were also intensified, and both paræsthesia and synæsthesia were noted on occasion. None of the subjects displayed the enhanced capacity for empathy characteristic of mescaline.

The emotional responses elicited during the period of maximum *dl*-3,4,5-trimethoxyamphetamine intoxication (3–5 hr. from the start of the experiment) were striking in their intensity. Anger, hostility, and megalomaniac euphoria dominated the subject's thoughts and conversation. Actual acts of hostility were not observed, but it was felt that, in at least two subjects, provocation would have precipitated homicidal violence. All subjects reported imagery, either patterned or scenic, with eyes closed. Recollection of past experiences did not seem to be enhanced, and intellectual performance appeared to be somewhat impaired. Once the plateau of intoxication had passed, return to normal was rapid. The subjects experienced no clouding of consciousness, and subsequent recall of events was excellent.

Due to the unexpectedly anti-social character of the response to larger doses of the drug (a response unobserved in more than 40 mescaline subjects), a warning concerning adequate supervision during experimentation with this new drug seems desirable.

Investigations employing the optical isomers, as well as structural homologues, of *dl*-3,4,5-trimethoxyamphetamine are in progress.

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The Conversion Ratio as a Discriminatory Test for Thyroid Activity in Fish

The rate of conversion of administered inorganic radioiodine into protein-bound radioiodine of the plasma has been used frequently to evaluate thyroid activity in mammals. The test is recognized as having good discriminatory power in higher vertebrates[1,2], but the relatively large sample of blood required for separation of serum by the usual methods has made the test impractical for small fish. A method is described here for determining protein-bound radioiodine as an *in vivo* test in fish of 30 gm. or more and as a terminal test in fish as small as 1 gm.

Each fish received an intraperitoneal injection of carrier-free iodine-131, the dosage depending on the weight of the fish and the detection instrument used. When using a scintillation well-counter, the instrument of choice, 0·1 μc. iodine-131 per gm. body-weight was sufficient. Blood sampling for *in vivo* determinations in anæsthetized trout were carried out by direct cardiac puncture with a ¼ c.c. heparinized syringe. Blood was transferred to a heparinized capillary tube and the vacant end of the tube plugged with 'Plasticene' or sealed with a small concentrated flame such as that of a propane torch. Blood may be obtained from very small fish by cutting off the tail and collecting the blood as it flows from the caudal artery into a heparinized capillary tube. Sealed tubes were centrifuged in a hæmatocrit centrifuge or in a 15-ml. bucket centrifuge fitted with hollow wooden adapters for the tubes. After separation of the cells, the tubes were scratched and broken between cells and plasma and the plasma was expressed into a 15-ml. centrifuge tube containing 2 ml. of 20 per cent trichloroacetic acid. The protein precipitate was stirred vigorously with a glass rod and centrifuged down. The supernatant containing the inorganic iodine-131 was decanted and saved. The precipitate was washed three times with 2-ml. portions of 2·5 per cent trichloroacetic acid, each time breaking up and stirring the precipitate and then centrifuging. All trichloroacetic acid washes, totalling 8 ml., were combined and saved. The precipitate was then dissolved in sodium hydroxide and diluted to the same volume as the combined supernatant washings. Finally, the radioactivity of both fractions was counted. Using the well-crystal scintillation counter, aliquots of supernatant and dissolved precipitate were pipetted into counter tubes and counted to 10,000 counts. An end-probe scintillation counter was occasionally used, and greatest sensitivity was achieved by securing the probe with crystal facing up in a lead castle and placing the fractions contained in a small beaker directly on the crystal. After subtraction of the background count, percentage of protein-bound iodine-131 is calculated as :

$$\frac{\text{Prot.-bound iodine-131 in counts per min. (precip.)}}{\text{Prot.-bound iodine-131} + \text{iodine-131 (combined counts of precip. and supernat.)}} \times 100$$

Serial determinations in rainbow trout (*Salmo gairdneri*) and starry flounder (*Platichthys stellatus*) have shown that protein-bound radiothyroxine in the plasma gradually increases relative to inorganic radioiodide until approximately the fourth or fifth day, after which it begins to fall. The rate of increase usually is most rapid just before the inflexion and represents the period when the greatest percentage