cysteine alone did not inhibit the enzyme, but only after being oxidized by the addition of cytochrome *c*. It remained to show whether cysteine or some other oxidation product of cysteine was the specific inhibiting substance.

The experiments outlined in Table I were set up to compare the degrees of inhibition of cystine and cysteine in equivalent concentrations, assuming that cysteine is oxidized to the dimer. In one pair, cytochrome *c* was added with the succinate after a 40-minute incubation and a 30-minute contact period. Cysteine without cytochrome *c* being present showed relatively no inhibition. Cysteine with cytochrome *c* present inhibited the enzyme to the extent of 34%. The oxidized dimer at half the monomer concentration and with cytochrome *c* present showed the maximum possible inhibition of 40% at M/2000 concentration (under the specific conditions noted). But in the absence of cytochrome *c* the cystine that was reduced was not reoxidized and the inhibition dropped to 35%. Cysteine with cytochrome *c* and cystine without cytochrome *c* were both lower than the maximum obtainable since the former had a time lag in the oxidation of the cysteine; the latter, nothing to reoxidize the reduced cystine. The results showed that the inhibiting substance in the cysteine-cystine system was cystine, but whether as the dimer or the free radical cannot be stated.

Summary. Cystine, without differentiating between the dimer and the free radical, inhibits the action of the succinoxidase system under the given conditions used in these experiments.

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On the Origin of the Fibers in the Pyramid of the Primate Brain.*

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That the pyramid (and corticospinal system) contains fibers which do not originate from the precentral gyrus has long been known. Monakow long ago pointed out that the distribution of the pyramidal cells of the cat was more extensive than the homologous region in the primate and published a figure[1] (his 34) showing a very extensive frontal and parietal origin for the human pyramidal system. The present author observed[2], "We have seen in our parietal material that a limited number of cerebrospinal fibers arise from that part of the parietal cortex immediately adjacent to the central fissure. This is by no means a novel observation and is correlated with the occasional finding of a few Betz cells in this region." The fact that corticospinal fibers arise from a location more extensive than the precentral gyrus was subsequently verified by other workers.[3] Few persons at that time questioned the belief that the corticospinal fiber arises from anything but the Betz cell and the extensive origin of the pyramidal system was regarded as due to a widespread distribution of these cells.

The Hoffs, using the degenerated bouton terminaux technic, conjectured that corticospinal fibers arise from cortex other than type 4, and Kennard, using the Marchi method, believed she was able to establish that such fibers arise from area 6. The present writer has not been able to substantiate such an origin for the system and Levin and Bradford,[4] using the cell degeneration technic, gave it as their opinion that few if any such fibers arise

* Aided by the Wm. J. Matheson Commission.

1 Monakow, C. v., *Die Lokalisation im Grosshirn*, Wiesbaden, 1914, *vide* S. 183 *et seq.*

2 Mettler, Fred A., *J. Comp. Neurol.*, 1935, **61**, 536.

3 Levin, P. M., *J. Comp. Neurol.*, 1936, **63**, 369.

4 Levin, P. M., and Bradford, K., *J. Comp. Neurol.*, 1938, **68**, 411.

from area 6 or even from the rostral part of area 4. According to them, 80% of the fibers come from area 4 and the remainder from areas 3, 1, 2, and 5 in the parietal lobe.

Lassek and Rasmussen[5] and Lassek[6] who first conclusively showed that the Betz cell is an unreliable criterion of the origin of the pyramidal tract. Lassek's subsequent work has confirmed and extended his original findings and it is now generally admitted that only a small part of the corticospinal system can be traced to such cells. Do the numerous non-Betz origin fibers arise from smaller cells in the region where the large cells are found? Do they come from other cortical regions (Peele[7] was of the opinion that they arose even from the back of the parietal lobe)? Is it true, as Marie and Guillain[8] suggested, that fibers, which they called parapyramidal, arising in the brain stem, enter the pyramids?

The answer which one gives to these questions will depend, to some extent, upon the techniques employed to study them and we may divide our observations upon such a basis.

Cell-degeneration Technic. If one cuts the corticospinal system and searches for chromatolytic or, if the degeneration time is longer, grossly abnormal cells in the cortex, it is very difficult to draw conclusions as to whether any particular cell is abnormal or to find such cells if they are dispersedly arranged. Moreover, doubt must always be entertained as to whether the obviously abnormal cells are specifically related with damage of the corticospinal system and nothing else. The present writer has not been able to draw any specific conclusions upon the origin of the non-Betz pyramidal fibers, from such material.

Marchi Method. If area 4 is removed and any of the Marchi methods are employed the amount of degeneration in the pyramids is so extensive that scarcely any normal fibers can be found. Obviously one cannot conclude from such evidence that some pyramidal fibers do not arise outside area 4.

If areas other than 4 are removed, few if any degenerated fibers are found in the pyramids of Marchi-stained material. There are exceptions to this rule. If a ledge of bone is allowed to press on area 4, if burrs are used in its vicinity, or if it is closely approached or the dura incorrectly sutured, true degeneration may result from that region even though not directly operated upon. Moreover, if the Swank-Davenport technic is employed, and occasionally with any Marchi method, a certain amount of degeneration may be found in apparently normal material. This may represent casual, inevitable pathology or be clearly artifactual in nature. Negative evidence, under such circumstances, means more than positive and, in the present writer's experience, no conclusive data of this type has been encountered to indicate that true degeneration of the pyramids ever results from lesions which are far from area 4.

Sheath Stains. If myelin stains of the classic type are used, no intact fibers can be seen in the pyramids if area 4 is removed and 6 months or so are allowed to elapse. If, however, one employs stains such as the Weil or Mahon, falsely positive results are obtained within such a degeneration period. These range all the way from the staining of a few, scattered fibers of variable caliber to a condition in which the entire pyramid is well though differently stained from the normal. Here again, then, negative are preferable to positive findings and the results agree with what one obtains with the Marchi technic.

Silver Stains. Most of the above difficulties are obviated by the use of any reliable silver technic. When such procedures are employed, and sufficient time for degeneration is allowed to elapse, markedly different results are seen after ablations of different cortical areas. Thus, if only the caudal parts of area 4 and the adjacent portion of area 3 are ablated (case J 141, the physiologic features of which have been separately reported[9]), practically all the large fibers in the pyramids disappear but the smaller, thinly-myelinated and non-myelinated fibers remain. If one examines

[5] Lassek, A. M., and Rasmussen, G. L., *Arch. Neurol. and Psychiat.*, 1939, **42**, 872.

[6] Lassek, A. M., *Arch. Neurol. and Psychiat.*, 1940, **44**, 718.

[7] Peele, T. L., *Anat. Rec.*, 1942, **82**, 44.

[8] Marie, P., and Guillain, G., *Rev. Neur.*, 1904, **12**, 697.

[9] Mettler, Fred. A., *J. Comp. Neurol.*, 1944, **81**, in press.

silver sections taken from congenitally abnormal brains, in which the telencephalon is largely absent but the infratentorial regions normal, no trace of a pyramidal system can be detected.[10] It is obvious, therefore, that Marie and Guillain's conjecture that fibers from the brain stem itself contribute to the pyramidal system must be incorrect, at least with regard to infratentorial levels.

We may now ask whether the diencephalon contributes any fibers to the system. If all the cortex and corpus striatum are removed from an animal (case J 31, the physiologic, cytologic, and myelinated fiber features of which have been previously reported[11]) silver stains again reveal no fibers in the pyramids. The same is true of silver examinations made upon a monkey lacking only cortex and putamen (case J 33, other studies of which have been published[12]). We can, in fact, state that the small pyramidal fibers are definitely of cortical origin for silver studies of the pyramids of our case 36, from which only cortex had been removed,[13] have also failed to disclose any sound pyramidal fibers in silver section.

Conclusion. Practically all the heavily myelinated fibers in the pyramids of the monkey's brain arise from the region of the cerebral cortex in which the gigantopyramidal cells of Betz are found. Since we know that all of these fibers cannot be accounted for as arising from such cells they must also come from smaller elements. The fact that Weigert material fails to show any fibers in the pyramids after ablation of the precentral gyri, does not prove that the pyramids are devoid of fibers for smaller elements can plainly be seen with silver stain. Since no fibers remain after removal of all of the cortex none of these smaller fibers can be attributed to an infrapallial origin.

[10] Marburg, O., and Mettler, Fred. A., *J. Neuropath. and Exp. Neur.*, 1943, **2**, 54.

[11] Mettler, Fred. A., *J. Comp. Neurol.*, 1943, **79**, 209.

[12] Mettler, Fred. A., *J. Comp. Neurol.*, 1943, **79**, 204.

[13] Mettler, Fred. A., *J. Comp. Neurol.*, 1943, **79**, 195.

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Effect of Pyridoxine on Activity of Quinine and Atabrine Against *Plasmodium lophuræ* Infections.

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In an investigation of the effect of large amounts of vitamins on the activity of quinine and atabrine in avian malaria it was found that massive doses of pyridoxine markedly inhibited the activity of these drugs against *Plasmodium lophuræ* infections.

Pekin ducklings weighing about 50 g each were inoculated intravenously with 10,000,000 erythrocytes parasited by *P. lophuræ*. The ducks were allowed to feed at will on a commercial starting mash. In all experiments quinine sulfate and atabrine dihydrochloride were administered as aqueous solutions into the crops by tube once daily for 6 days beginning on the day of inoculation. Pyridoxine hydrochloride was given in the same manner in most of the experiments but as is indicated on the accompanying tables it was in certain cases administered subcutaneously. Since both quinine and pyridoxine are excreted quite rapidly they, although given individually, were always administered within an interval of about 30 minutes. Blood smears were made on the seventh day after inoculation and the number of parasitized erythrocytes per 10,000 erythrocytes was determined.

Pyridoxine when given in a large daily dose produced almost complete inhibition of the