addition to it of axones derived from the neuro-epithelium of the transplant. The ingrowth of the enlarged olfactory nerve trunk into the cerebral hemispheres results in an increase of the cellular content of the olfactory bulb amounting to approximately 30 per cent. No such increase occurs in those instances where the transplant has made no contribution to the olfactory nerve.

In the experimental embryos where the transplant did not fuse with the placode of the host, the outgrowing fibers from the neuro-epithelium of the transplant pursued either one of two courses. In a majority of cases they established connection with the pars dorsalis thalami with resulting hyperplasia of a restricted region in the central gray. Several experiments resulted in the axones from the transplant joining the ophthalmic branch of the Vth cranial nerve, ascending along it and terminating in the ophthalmic ganglion. Here again hyperplasia of the cellular elements in the ganglion occurred.

It is suggested that the growth of axones into a field of growing neuroblasts is a factor in producing cell proliferation, the degree of which is dependent upon the number of ingrowing nerve units. More than the normal number of these can produce hyperplasia of the region.

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The effect on the involuntary nervous system of arsenicals and the salvarsan group.

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I.

Investigations on the effect of nonspecific therapeutic agents by one of us (E. M.) have shown that these all become effective through their action on the involuntary nervous system. These findings were mainly obtained from observations of intradermal injections of Aolan, a nonspecific lact albumin preparation. After these injections were administered intradermally, an acute

leucopenia of the peripheric vessels becomes evident for approximately half an hour. Extensive studies on intradermal injections led to the explanation of these phenomena. Every acute decrease of leucocytes in the peripheric vessels corresponds with an increase of leucocytes, more particularly of the neutrophile polynuclear type, in the vessels of the splanchnic area. This acute displacement of leucocytes is a manifestation which shows that there is a stimulus operating upon the parasympathetic portion of the vegetative nervous system. The cause of this stimulus may originate in different organs. The result, especially in the described acute leucopenia—possibly there are also other secondary results, as yet unknown to us—is a vasodilation in the visceral region. It is assumed from earlier experiments that this vasodilation in turn causes an increase in leucocytes in the distended vascular region and a corresponding impoverishment, or leucopenia in the peripheric blood.

II.

Further studies upon a similar acute leucopenia observed immediately after intravenous injections of salvarsan and neosalvarsan in man became possible in connection with the above findings which revealed that such a decrease is always a result of a stimulation of the parasympathetic nervous system.

The first observations along these lines have shown that following every injection of salvarsan in a human being there is a decrease in the leucocyte count; this decrease as a rule does not exceed 1/3 the original count and does not persist longer than 10 minutes. In some patients, presenting reactions immediately after treatment (so-called table reactions) the decrease of leucocytes was greater than generally observed; the decrease in such cases frequently amounting to 7/10 and more. Sometimes unusually low counts (one to two thousand) were observed. The leucocyte count increased again as the reaction gradually disappeared. The results obtained from observation of clinical material will be found in another article.

These changes of the leucocyte curves became more interesting when it was found that after injections of silver salvarsan there was practically no difference in the numbers of white blood cells before and after injection. This observation together with the well-known fact that the so-called nitritoid crisis is very

rarely observed after injections of silver salvarsan showed that these manifestations are closely related to the immediate condition of the involuntary nervous system. Only patients presenting angioneurotic symptoms after injections of salvarsan showed an exception to this rule in more or less decreasing leucocyte curves, also after administration of silver salvarsan; thus proving that in these patients there must be a previous disturbance or hypersensitiveness of the involuntary nervous system. It is not known whether this disturbance is caused constitutionally or by the syphilitic infection. The involuntary nervous system causes not only the acute blood changes but also the manifestations known as symptoms of angioneurotic shock.

The remarkable difference in the effect of these two members of the salvarsan group on the leucocyte count led to studies in man which will be published as soon as our series of investigations has been completed. Another series of studies was undertaken concerning the effect of toxic and unusual compounds of the salvarsan group on rats. The first experiments showed the effect of fatal doses of properly alkalinized salvarsan and silver salvarsan. The injection of fatal doses did not produce any fundamental difference in the described curves of the blood count while the usual dose given to rats produces an effect similar to that in man. The results of experiments with salvarsan solutions not employed in human therapy were quite different. The injection of the *monosodium salt of* salvarsan is known to be injurious to man in many instances; the reaction following such injections are often severe and dangerous. In experimenting with these solutions in rats it was found that a large decrease of the leucocyte count took place. Comparison of the observations after injections of this drug with those following injection of the *disodium salt of* salvarsan showed that the decrease of leucocytes in much larger in the case of the *monosodium salt* than in that of the *disodium salt.*

Further studies were undertaken with *concentrated acid salvarsan* solutions. It is known, that concentrated acid salvarsan solutions are usually fatal in humans and have been responsible for the death of many patients. Experiments in rats also demonstrated a considerable fall in the number of leucocytes after giving such acid preparations. These experiments were not always uniform; some of the animals even dying during

the injection. In such cases no leucocyte reaction was observed. If death did not result immediately the change in blood cells was striking, their number at times decreasing to below one thousand.

Specimens of blood were taken from the tail vein and from the heart of the living animal under controlled conditions. Normal counts were made in every instance at periods approximately 30 seconds apart. Specimens of blood were obtained from the liver of the animals which died as a result of the shock.

III.

The experiments in rats together with the observations in man following the injection of various salvarsan preparations in connection with the earlier findings on the relation between leucocytes and the involuntary nervous system led to the following conclusions: Every intravenous injection of salvarsan is followed by a slight decrease of leucocytes in the peripheric vessels of the entire body indicating a small reaction of the involuntary nervous system. The decrease is great in patients who develop manifestations of the so-called nitritoid crisis.

Intravenous injections of silver salvarsan are as a rule not accompanied by any change in the leucocyte count, thus indicating that there is no reaction or disturbance of the involuntary nervous system or of the vascular system of the body.

Fatal doses of the salvarsan solutions usually employed do not produce fundamental differences in the reaction of the autonomic nervous system. Monosodium salt and acid solutions of salvarsan always produce a great disturbance of the involuntary nervous system. The parallelism of the leucocyte count and the frequency and character of the clinical reactions following these different preparations shows the relation between the manifestation in the blood and the reaction so far characterized only by the clinical picture. Further it shows that fatal or dangerous disturbances of the autonomic nervous system are not caused by the drug itself but by the use of solutions whose physical characteristics are not properly adjusted to the body fluids, or by previous disturbances of the involuntary nervous system in certain individuals.