asepsis is observed, holds out the promise of good results.

(2) That cancellous grafts, as malleable bone forming media tend, in association with graduated movements and accurate splinting, to an earlier restoration of function and symmetry than do grafts of compact bone.

I am indebted to Lieutenant-Colonel S. R. Christophers, C.I.E., I.M.S., Director, and the Officers of the Central Research Institute, Kasauli, for the pathological examination and the microphotograph of the tumour material, and to the Editor, *Guy's Hospital Reports,* for permission to republish.

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A PRELIMINARY NOTE ON THE PHARMACOLOGICAL ACTION OF SOME ORGANIC-ANTIMONY DERIVATIVES.*

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DURING the last decade a number of organic-antimony derivatives (aromatic) have been introduced for the treatment of certain tropical diseases of protozoal nature. The origin of these aromatic antimonials was due to the work of Michaelis and Reese whose investigations led to the preparation of triaryl-stibines. Later, Grignard's reaction gave rise to the preparation of triphenyl-stibamines. Most of the present development of the organic-antimony derivatives, however, is due to the work done by Chemische, Fabrik Von Heyden who discovered the process of introducing into the aromatic nucleus the antimonial group through the agency of the diazo-reaction. Great impetus was thus given to the synthesis of aromatic antimonial drugs and most of the antimony analogues of the aromatic arsenical drugs such as atoxyl, salvarsan, etc., were prepared. From aniline by diazo-synthesis it was quite easy to prepare phenylstibinic acid and then para-amino phenylstibinic acid (p-stibanilic acid) which is the antimony analogue of p-arsanilic acid. Its sodium salt, sodium-para-amino-phenylstibinate (or sodium p-stibanilate), is the antimony analogue of the arsenical compound known as atoxyl or arsamin (sodium p-arsanilate). This compound was later given the name of *stibamin* by Dr Brahmachari from its analogy to the corresponding salt of arsenic which is called *arsamin*. A derivative of this sodium acetyl-p-amino-phenyl stibinate was called *Stibacetin* which was one of the earlier members of the aromatic series to be used in therapeutics against leishmaniasis. This was put on the market by Messrs. Allen and Hanbury under the trade name of *Stibenyl*. This compound is soluble in water, is stable and does not irritate the tissues to the same extent as do some of the organic-antimony compounds. Unfortunately, however, it did not prove of any great therapeutic value in kala-azar in this country. The sodium salt of p-amino-phenyl stibinic acid, or sodium p-amino-phenyl stibinate (*Stibamin of Brahmachari*) is also a soluble compound which, though therapeutically active, is unfortunately not very stable. Its therapeutic application was, therefore, limited. The carbamide derivative of p-amino-phenyl stibinic acid was then prepared by Brahmachari by warming p-amino-phenyl stibinic acid suspension in water and urea, until the whole of the acid is almost dissolved; this is concentrated on a water-bath and the salt is precipitated by the addition of alcohol. The resultant substance was called *urea-stibamine* and is a pentavalent compound of antimony. Brahmachari believes this substance to be not a urea salt of stibanilic acid but a substituted urea. Henry has, however, criticised and doubted the constitutional formula given by Brahmachari.

The combination of urea with p-amino-phenyl stibinic acid renders this compound more stable and soluble (p-amino-phenyl stibinic acid is not soluble) and at the same time more efficacious therapeutically. It is a well-known fact that when quinine is combined with urea, its solubility and diffusibility is considerably increased and the resultant compound is able to penetrate better into the tissues; its local anæsthetic action is also much enhanced. The same probably happens in the case of *urea-stibamine*. Better penetrability of the compound probably accounts for the superior therapeutic results obtained by this drug as compared with the previous compounds. There are two brands of *urea-stibamine* on the market. Our chemist, Mr. N. R. Chatterjee analysed these samples of *urea-stibamine* and found them for all practical purposes to be the same. Dr. Napier has used both these brands

* Whilst this issue was in the press an announcement has been made that Dr. Brahmachari has obtained an injunction to restrain the Union Drug Company from using the name urea stibamine as a designation of the carbamide salt of p-amino-phenyl-stibinic acid.

The effect of this judgment is to give to Dr. U. N. Brahmachari the sole right to the use of the name urea-stibamine for the purposes of manufacture and sale of the drug.

We had hitherto been under the impression that the name urea-stibamine was a scientific description of a valuable drug which had been prepared by a medical scientist for the use of the whole world. According to the recent judgment it is only the process of manufacture which is common property, the name urea-stibamine is held to be a fancy trade designation, which Dr. Brahmachari alone is entitled to use.—EDITOR, *I.M.G.*

in the Carmichael Hospital for Tropical Diseases and the clinical results were equally good; I will show later in this paper that their pharmacological reactions in animals are almost identical.

Von Heyden a few years ago, introduced a compound, metachloro-para-acetyl-amino-phenyl-stibinate (Von Heyden 471) to which they gave the trade name of *Stibosan,* and later they introduced another compound, an amino salt of para-amino-phenyl-stibinic acid. Both these compounds have given very good results in kala-azar in Dr. Napier's hands. They are more efficacious than some of the earlier organic-antimony aromatic compounds such as *Stibenyl,* and are as good as *urea-stibamine.* A number of other organic-antimony compounds (aromatic) have been put on the market lately and some of them have been tried in the treatment of kala-azar with success. One of these compounds is p-amino-phenyl-stibinic acid urea-glucose, which has been prepared by the Union Drug Company, Limited, and they have given the compound the following formula $C_6 H_{11} O_5 NH\text{-}CO\text{-}NH C_6 H_4 SbO (OH) (ONH_4)$. This compound has been given the trade name of '*Amino-stiburea*' and Napier has obtained good results with it in kala-azar. Yet another compound has been prepared to which the name of '*Novo-stiburea*' has been given, but its composition has not yet been disclosed. This compound is claimed by the makers to be quite stable; it can be dissolved in tap-water, its solution can be sterilized by boiling and it is said to have good keeping properties. If the compound is really stable and as effective therapeutically as *urea-stibamine* or *Stibosan* it will make a distinct advance in the treatment of kala-azar. Most of the antimony compounds in use at present are unstable in the air even in a solid condition and in solution they change very rapidly.

These compounds are of great importance in the treatment of kala-azar and are being injected intravenously. No attempt has been made, so far as I am aware, to work out their pharmacological action. As these compounds are being used extensively in this country, I have undertaken to work out their pharmacological reactions in animals. In this paper the results of my observations have been summarised; but the detailed work with the graphs will be published later, in a more technical journal.

The Pharmacological Action of Antimony Compounds.—The pharmacological action of these compounds was investigated on cats. The animals weighed 1,800 to 2,500 grammes and were anæsthetized with urethane, a small amount of ether being given when necessary. The blood pressure was recorded by putting a cannula into the carotid artery and the volumes of the intestines, the spleen the kidney and the limb were recorded in the manner usual in pharmacological tests. The pulmonary pressure was recorded by the delicate method described by Jackson and Rapp. The drugs were injected into the femoral vein in doses ranging from 10 mgm. to 100 mgm. The 10 mgm. dose was, however, found to be too small to produce any effects, while with 100 mgms. the reaction was severe and often the animal succumbed. Doses of 50 mgm. gave good reactions and we used this quantity in most of our experiments. The results obtained are shewn in the following table:—

Table summarising the pharmacological action of Antimony Compounds.

	Sodium antimonyl tartrate.	"Urea-stibamine" Both brands.	"Stibosan" Von Heyden's 471.	"Amino-stiburea" Union Drug Co.	"Novo-stiburea" Union Drug Co.
1. Blood Pressure, Systemic.	Slight fall	Marked and lasting fall. Heart slow and irregular. Pressure regains its normal level.	Great fall, may go down to zero. Heart very irregular. Pressure slowly regains its normal level.	Slight fall of B. P.	Slight fall.
2. Blood Pressure. Pulmonary.	Fall followed by slight rise.	Marked and sustained rise.	Marked and persistent rise.	Marked rise.	Rise.
3. Cardiometer and Myocardiograph results.	Marked momentary depression.	Slight but lasting depression.	Slight and persistent depression.	Slight and persistent depression.	Slight depression.
4. Isolated Heart (Mammalian).	Marked depression.	Momentary depression. Relaxation of ventricles.	Depression. Heart irregular.	Depression. Relaxation of ventricles.	Slight depression.
5. Respiration ..	No effect, sometimes slight stimulation.	Stops momentarily, then depressed. Amplitude decreased.	Stops longer, then restarts.	No effect.	Slight quickening.
6. Spleen volume	Increase.	Marked increase. Rhythmic movements.	Marked increase. Rhythmic movements.	Marked increase. Rhythmic movement.	Increase.
7. Intestinal volume.	Decrease	Decrease.	Decrease	Decrease	Decrease
8. Kidney volume	Decrease	Decrease	Decrease	Decrease	Decrease.
9. Limb volume ..	No effect	Slight decrease	Slight decrease	Slight decrease	Decrease.

Discussion of the Table.—A perusal of the table will show how the blood pressure, respiration, and different organs react to intravenous injections of antimony compounds. All the compounds with the exception of *Novo-stiburea* produced a fall in blood pressure immediately after injection, as will be seen from a glance at the horizontal column No. 1. The two brands of *urea-stibamine* we tested gave a marked depression amounting in some cases to 20 to 25 mm. of mercury. With *Stibosan* the fall of blood pressure was even more marked being as much as 50 mm. of mercury; in some cases the pressure went down to zero, the animal at the same time showed marked symptoms of collapse. The heart became slow and irregular but gradually recovered and the blood pressure came to the normal level. Dr. Napier informs me that occasionally he gets a case in which sensitisation develops, and suddenly after 5 or 6 injections, injection of the usual quantity of any of the pentavalent antimony compounds, produces marked collapse. I had a patient who had an injection of a small therapeutic dose of *Stibosan* for the first time and who showed all the signs of severe collapse.

All these substances have a depressant action on the heart and they relax the ventricles in the same way as do the cinchona alkaloids; this will be seen by a perusal of the horizontal columns Nos. 3 and 4. With regard to the effect on the pulmonary blood pressure recorded in horizontal column No. 2, there is a marked rise in pulmonary pressure with all the organic-antimony compounds which we have tested. It is worthy of note that arsenical compounds such as salvarsan also cause a marked rise of pulmonary pressure, and this is of interest in connection with the "nitritoid crises" which are produced by administration of this drug. It is quite likely that the symptoms which occur in patients after injections of antimonial compounds may be due to changes occurring in the pulmonary circulation. This point is under investigation. In horizontal column No. 5 will be seen the effect of intravenous injections of antimony compounds on the respiration. *Urea-stibamine* and *Stibosan* produce a more marked effect on the respiration than sodium antimony tartrate, *Amino-stiburea* and *Novo-stiburea*. With the two former drugs the respiration may cease for 10 to 30 seconds, but it is not permanently paralysed and quickly regains its normal amplitude.

The effect of antimony salts on the spleen is recorded in horizontal column No. 6. There is a well marked increase in size in all cases; with *urea-stibamine* and *Stibosan* this action is more marked than with tartar emetic. Is it possible that this increase in spleen volume has something to do with the therapeutic effect produced by these compounds in curing leishmaniasis? The spleen is a reservoir of parasites and the influx of blood charged with antimony into this organ might contribute towards the destruction of the parasites and cure of the disease. Horizontal columns Nos. 7, 8 and 9 show the action on the intestine, kidney and limb volume.

I have much pleasure in acknowledging the help that I have received from Captain Premankur De and Mr. Nihar Ranjan Chatterjee in the course of this research.

SUMMARY AND CONCLUSION.

The action of a number of organic-antimony derivatives has been tested on cats. All these substances have a more or less depressing effect on the heart, circulation and respiration. The systemic blood pressure falls, whilst the pulmonary blood pressure rises. The volume of the spleen is markedly increased, while the volume of the intestine, kidney and limbs decreases.

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AN ENTOMOLOGICAL EPISODE OF THE EAST AFRICAN CAMPAIGN.

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DURING the year 1915, I was stationed at a large post in East Africa in the crater-like depression of an isolated volcanic mountain. This mountain had been held for some months by the Germans, and when we occupied it, we found ourselves obliged for reasons of defence to place part of our troops upon the site of the old German camp. We had not been there for many days before we found that the site was heavily infected with jigger fleas, left doubtless by the African troops and porters of the German force.

Our men, mainly European and Indian troops who had little or no previous experience of the jigger, rapidly became infected to an alarming extent, and in a few weeks' time nearly half our garrison was unfit to march. Everything that could be thought of was done. All troops wore boots and socks and were warned not to put their naked feet to the ground. Tent flaps were raised during the day to allow sunlight to beat upon the floor. Tent sites were frequently changed, and a weekly inspection of the men's feet was instituted and all jiggers removed and killed. Still the disease continued. Raised beds constructed from brushwood were built inside the tents and the floors leeped to reduce dust. Kerosine oil emulsion was sprayed on the floors of tents and huts, and the men's socks were treated with the same solution. Facilities were