THE MODERN TREATMENT OF LUPUS ERYTHEMATOSUS.*

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THE subject I propose to discuss here is the treatment of lupus erythematosus by means of certain compounds of gold. Up to recent years there was no cutaneous complaint which was more disappointing to deal with than this, but since 1922 the position in regard to its therapeutics has been very greatly improved. Before going into the details, I think it will not be a waste of time if I develop shortly the position of this disease in relation to tuberculosis of the skin. Every practitioner is, of course, well acquainted with lupus vulgaris, the common manifestation of tubercle of the skin. The two names, lupus erythematosus and lupus vulgaris, both with the common denominator lupus, express the clinical similarity of the two conditions, although it is true that it is easy enough to diagnose typical cases of the one from the other.

Lupus vulgaris is a disease of childhood and youth, scarcely ever beginning after the age of 25, and is characterized by the well-known apple-jelly nodules. It is prone to ulceration and has no tendency towards symmetry. Histologically it is distinguished by the usual histology of tuberculous tissues—giant cells, imperfect fibrous tissue, etc. On the other hand, lupus erythematosus is rare before the late twenties, it has no apple-jelly nodules, and clinically it appears merely as a permanent scaly erythema and has a great tendency towards a symmetrical distribution. This tendency leads to the well-known "butterfly" or "bat's wing" formation, stretching from cheek to cheek of the patient, involving the nose *en passant*. In bad cases it often affects the scalp, and, especially when of an acute type, the hands and feet in addition. Histologically it presents no feature beyond a small round-cell infiltration round the blood vessels. But there are intermediate cases which are extremely hard to diagnose accurately. Even Dr. Sequeira, who had an unrivalled experience at the London Hospital in lupus, used at times to confess himself at a loss. It is often very hard to make out the apple-jelly nodules, which may be very small in certain kinds of lupus vulgaris, and in an early case of lupus erythematosus the typical symmetry has not yet had time to develop itself. Lupus erythematosus is, I believe, a good deal commoner than is generally supposed. There are many cases of permanent patchy and scaly erythema on the face which are really cases of this disease but go unrecognized. On the other hand I have had a case myself which, when I first saw it, I thought was typical lupus erythematosus, and which I treated as such, but when the erythematosus factors had subsided typical lupus vulgaris was revealed.

The great problem, to which much work and study have been devoted, is the relationship of lupus erythematosus to tuberculosis. As is well known, in addition to real tuberculosis of the skin, such as lupus vulgaris and tuberculoderma, there is an important class of eruptions known as tuberculides, which are supposed to differ from frank tuberculosis in that they do not contain the bacillus itself but are due to the toxins produced by that organism. Such are the eruptions known as lichen scrofulosus, acne scrofulosorum, and Bazin's disease, and possibly the rare acne agminata, and those indefinite lumps known as sarcoids. A large quantity of work has been done to show that lupus erythematosus should really be reckoned as a member of this class. It is true that the subjects of the disease, especially in the acute form, often develop tuberculosis of the lung. Sometimes they give positive reactions to the various tuberculosis cutaneous tests. Ramel, for example, finds that tuberculin gives a positive reaction when injected into a patch of lupus erythematosus. On the other hand, the positive reaction is by no means universal. A good many patients with acute lupus erythematosus have actually died without exhibiting any signs of real tuberculosis, either during life or post mortem. Barber thinks that there are

two kinds of lupus erythematosus, one of which is a tuberculide, but the other a streptococcide, and due to some focal infection, most often in the tonsils. He has published cases in which the patients were cured by excision of the infected tonsils, and others in which a positive reaction was obtained by the inoculation of a streptococcal vaccine. The issue is still doubtful.

The form of treatment which I now propose to discuss rather lends support to the tuberculide theory. Gold was first tried in the treatment of tuberculosis almost a hundred years ago, and at one time injections of gold cyanide, of course appropriately diluted, were employed in the treatment of lupus vulgaris, but it was not until 1922 that Martenstein¹ published a series of forty-two cases of lupus erythematosus which he had treated with a new organic gold compound known as krysolgan. This consists of a benzene ring to which the gold is attached through the medium of sulphur. In his results he claimed 66.5 per cent. cures, most of the remainder greatly improved, four unaffected, and, it is true, four made worse. These figures were far better than had ever been obtained before in the treatment of the disease. A few patients had seemed to improve under quinine, either given by the mouth or intravenously injected. Others had been reported as favourably influenced by local application of carbon dioxide snow—a painful, barbarous, and uncertain method, which I myself had long discarded—and a few more cases seem to heal spontaneously. On the whole, however, the disease was a very disappointing one to deal with.

Naturally, after Martenstein's work, the gold treatment was tried by other dermatologists, but it did not spread very quickly, at all events in this country. Even in 1926 an authoritative article by one of our leading lights on the modern technique of treatment of this disease never even mentioned it. However, in the 1927 meeting of the British Medical Association at Edinburgh, Dr. Semon read an article on the treatment by krysolgan, and it appeared from the subsequent discussion that a good many British workers had then tried it, but with results hardly comparable with those of Martenstein. No one claimed more than 30 per cent. of absolute cures, and a good many cases remained uninfluenced.

Meanwhile, however, another compound of gold had become conspicuous in the therapeutic world as a valuable aid in the treatment of tuberculosis of the lung. I refer to sanocrysin. This, as of course you are aware, unlike krysolgan, is an inorganic compound, and is really a double thiosulphate of gold and sodium, very analogous in composition to the well-known "hypo" which we use to fix our photographs with. Originally discovered in 1845, it remained in obscurity until about 1918, when Moellgaard took it up as a treatment for tuberculosis. It occurred to some of us who were disappointed with the results obtained from krysolgan, and who hoped for something better, that possibly, if lupus erythematosus were really allied to the tuberculides, a compound which had shown itself valuable in the most fatal of all tuberculous affections might be of great use in a condition of much lower virulence, but somewhat of the same nature. I tried it myself for the first time on a patient, a man, aged 55, who had made some improvement with krysolgan, but subsequently hung fire. His progress was dramatic. Within two months the whole disease, which had been extensive, causing great swelling of the nose, with large patches on both cheeks, the upper lip, and chin, had disappeared, leaving only a few slight and inconspicuous scars, and I had the pleasure of showing him at the October, 1928, meeting of the Dermatological Section of the Royal Society of Medicine, where the other members had no hesitation in admitting that the disease was cured. I also showed three other patients treated in the same way at the same time. But although the idea of trying sanocrysin occurred to me spontaneously, I cannot claim to have been actually the first to use it in this way. Schamberg and Wright² had published already in 1927, in the *American Archives of Dermatology*, a series of cases successfully treated with various gold compounds, including sanocrysin, and I have no doubt that other workers were using it also about the same time. Indeed, it is almost inevitable that, after trying krysolgan, one should cast about for other similar bodies to carry on the good work, if krysolgan has failed.

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Both these drugs are given intravenously. In most cases this presents no great difficulty, but, as everybody knows, there are patients who seem absolutely destitute of suitable cutaneous veins. Both these compounds are freely soluble in water, and as they are always sent out by the manufacturers in sealed glass ampoules, it is very convenient to dissolve them *in situ* and to draw the solution straight into the syringe to be used for injection. They are both very unstable in solution, and the solution must on no account be kept from day to day. Sanoerysin solution is quite colourless, but it soon precipitates metallic gold, not as a shining metal, but in the form of an impalpable black stain, which it is difficult to remove wholly from the wall of the syringe, and which also frequently leaves a black mark in the skin of the patient at the site of repeated injections. The dose of these two compounds is very different. That originally prescribed for krysolgan was initially 0.015 grain, and the maximum dose was 1.5 grains. In the case of sanoerysin, however, we begin at 0.05 gram, and as much as a whole gram of sanoerysin may be given in one injection. Lately, however, I have given up doses larger than 0.5 gram. When one considers that there are fifteen grains in every gram, it follows that, on the whole, the dose of sanoerysin prescribed is from ten to fifteen times as great as that of krysolgan. Probably much larger doses of krysolgan could be given to many patients with impunity, but one hesitates to exceed the limits laid down by the manufacturers. Personally, I have never had any toxic symptoms following its administration, but several instances where these have occurred have been published. Gold is, as we are all aware, a metal powerful both for good and for evil, and although the benefits from the use of sanoerysin in lupus erythematosus are unquestionable, and I believe that its reputation among those who treat phthisis is gradually becoming enhanced, there is no doubt that it is not a drug to be put in the hands of children.

The clinical response in the administration of these drugs is, as might be expected, by no means uniform for every patient. My practice is always to begin with krysolgan, and a very small dose—that is, 0.015 grain, and gradually work up by weekly doses to 1.5 grains. Not infrequently a distinct improvement is seen after the first one or two doses, but, on the other hand, after about six weeks' treatment progress frequently slackens. I then switch on to sanoerysin, beginning with a dose of 0.05 gram, and gradually work up to either 0.25 or 0.5 gram, occasionally even to a whole gram. Patients who have been favourably affected by krysolgan almost always improve further under sanoerysin. Sometimes the improvement is preceded by a local reaction occurring immediately after the injection, during which the affected areas become redder and slightly heated. In other patients the areas fade gradually and the scaling diminishes without any temporary exacerbation.

As to the ultimate result of this form of treatment, I regret that I have no proper statistical analysis of my cases to set out. I suppose in the last three years I have treated about forty cases. I can remember ten certainly which have been discharged as cured, and have remained cured. The great majority of the remainder have been greatly improved. Some of the lesions have cleared up completely, although perhaps one may remain obstinate or, after apparent cure, relapse has taken place. This much I think I can claim conscientiously, that in every case except one the disease has been arrested and has ceased to spread. When I remember the cases which I used to see in former times, and the inexorable way in which the disease used to invade and destroy the complexions of nice-looking people (and you must remember that lupus erythematosus is commoner among women than among men), I think that much credit must be attributed to the gold treatment. I mentioned above one patient who had grown worse under krysolgan and sanoerysin. Finding that this treatment was unsuccessful I tried neo-silver salvarsan, and I am happy to say that, under this, considerable, and I believe permanent, improvement has taken place. In this case the disease was chiefly on the hands.

Additional evidence of the value of the gold treatment of lupus erythematosus is afforded by the action of the manufacturing chemists. Imitation is the sincerest form

of flattery, and since krysolgan was introduced by Schering, other manufacturers have imitated and claim to have improved upon it. There are quite a number of other organic gold and sulphur compounds now on the market, made by various chemists. Among these I may mention aurophos, triphal, lopien, allocrysin. Schering has lately introduced one which is claimed to be a great improvement on krysolgan; it is called solganol, and, like all the others, is said to have increased therapeutic value combined with less toxicity. The maximum dose may be as much as a whole gram, but I have as yet had no personal experience with it.

I must not conclude without mentioning some of the possibly unpleasant effects of these compounds. One, very frequent but unimportant, is a metallic taste in the mouth immediately following the administration. This is a phenomenon common after the injection of many metallic drugs—for example, salvarsan, antimony, and sodium cacodylate. Some diarrhoea occurs occasionally, and there may be a febrile reaction, which soon passes off. More serious are the effects on the skin and mucous membranes. A follicular pruritic eruption is not uncommon, and unless this be regarded as a danger signal and the administration of gold be immediately ceased, it will probably be followed by a generalized exfoliative dermatitis. One such case has occurred in my experience, and gave me considerable anxiety for nearly a month, but it ultimately cleared up, and with it the erythematosus. Another serious complication may be a troublesome and painful stomatitis with a very sore tongue. This may be so bad as to interfere with swallowing and cause the patient to refuse food. In lupus erythematosus this is not of vital importance, but when it occurs in phthisical patients may do great harm.

There is one way in which the risk of the unpleasant accidents may be minimized. All these toxic effects are probably the result of the fixation of gold in the liver cells. If the liver cells are fully occupied by some harmless or beneficial substance they will not be able to take up the metal, consequently it is a wise precaution to give patients who are being treated in this way plenty of dextrose a few hours before each injection. This gives the liver something to do and prevents it getting into mischief. In addition, it is wise after patients have had several injections of their maximum dose to lengthen the spaces between doses to two, three, or even four weeks; and one is encouraged to do this by the fact that often improvement continues to make progress as long as three weeks after the last injection.

I myself feel that gold will one day be held to be at least as valuable in tuberculosis as mercury is in syphilis, and although the time is not yet, I hope I have shown that this is a promising field for further work.

REFERENCES.

- ¹ *Klin. Woch.*, 1322, p. 2235. ² *Amer. Arch. of Derm. and Syph.*, xv, p. 119.

THE STRUCTURE OF THE HUMAN ERYTHROCYTE.

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IF we accept the definition of structure as "the mutual relation of the constituent elements of the whole as determining its peculiar nature and character," and if we remember that cytological structure is brought into evidence only by alteration of the physico-chemical properties of various parts of the cell contents by the action of reagents, then no apology need be tendered if, to render the constituent elements of the erythrocyte visible, an unusual method is adopted.

Walker and Allen (1927) have shown that Golgi bodies and chondriosomes can be artificially produced by adding lipins—lecithin and cephalin—to certain colloidal and protein mixtures and subjecting them to the same processes as are utilized for the demonstration of Golgi bodies in cells; and Walker (1928) has made out an excellent thesis for the study of these artefacts as a guide to variations of the physiological state and pathological conditions. He has shown that saturation or oxidation of the lipins produces similar pictures in the artificial emulsions as in certain cell states.