CLINICAL COMMENTARY ON STUDIES OF HISTOLOGIC CHANGES IN ORGANS INDUCED BY ARSPHENAMIN, BY NEO-ARSPHENAMIN AND BY MERCURY

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The elaborate studies carried out by my colleagues, Drs. Kolmer and Lucke, on the histologic changes produced in the organs of experimental animals by arspfenamin, by neo-arsphenamin and by mercury are of interest and importance.

Scientific therapeusis presupposes a definite knowledge not only of established clinical results but likewise of the pharmacologic and toxicologic effects of remedies. A prolific literature has grown up on the clinical aspects of arspfenamin and neo-arsphenamin, but our knowledge of the pharmacology and toxicology of these complex compounds, as well as their fate in the human economy, is far from complete.

One of the fundamental principles of the new science of chemotherapy is that a chemical compound in order to be of practical value in the treatment of an infectious disease must have a greater affinity for the parasite than for the body cells, and the greater the discrepancy, the more valuable is the drug. In other words, there should be a large latitude of safety between the *dosis therapeutica* and the *dosis toxica seu lethalis*.

All powerful drugs doubtless bring about some structural changes in the cells of certain organs. When these structural changes are minimal no material interference with the integrity of function is induced. Where, however, severe or massive damage results organic insufficiency may be brought about, in some cases to such an extent as to lead to a fatal result.

In considering the structural changes induced by therapeutic doses of arspfenamin, neo-arsphenamin and mercury, we must remember that many infectious diseases likewise induce structural changes and organic restitution takes place. Influenza, typhoid fever and other infections may, for example, produce focal necroses in the liver, without ultimately interfering with proper functioning of that organ. Other infections, notably scarlet fever, may cause severe changes in the kidney, and yet restoration to healthy activity commonly results. It is well, however, to know what organs bear the brunt of the attack

when these powerful drugs are administered in order that we may watch symptoms referable to these organs and thus intelligently guide ourselves in the treatment. It should not be forgotten that in the treatment of a difficult disease like syphilis prolonged treatment is necessary and repeated organic insults, unless carefully watched, may lead to unfortunate results.

CLINICAL EXPERIENCE AND PATHOLOGIC FINDINGS

Let us consider to what extent clinical observation corresponds with the microscopic studies here discussed in elucidating the toxicologic effects of arsphenamin, neo-arsphenamin and mercury.

The studies carried out by Kolmer and Lucke indicate that the arsphenamins produce demonstrable effects chiefly on the liver, suprarenals and the blood vessels, and mercury chiefly on the kidneys and brain. The arsphenamins would appear to have a special affinity for the organs referred to—a hepatotropism, an adrenotropism and a vasculotropism. Mercury possesses a nephrotropism (an observation long known) and apparently a cerebrotropism, an observation which is as far as we know, new.

Do these biochemical affinities throw any light upon the toxic phenomena following the use of these drugs?

Space will not permit a discussion of the various reactions which from time to time follow the use of the arsphenamins. A large literature has already accumulated on this vexed subject. To mention briefly only the immediate nitroid reactions conjures up to the considerable diversity of opinion on the causation of these phenomena. Within the scope of this communication it might be pertinent to inquire whether the influence on the suprarenals and the chromaffin cells observed by Kolmer and Lucke, might bear any relationship to some of the symptoms of the nitritoid reaction. The most characteristic phenomenon of this syndrome is a pronounced vasoparesis followed in some cases by a great fall of blood pressure.

May this not in some cases be due to an inhibition of the production or secretion of epinephrin? It is not suggested that these reactions are usually due to the effect of the drug on the suprarenals, but the fact cannot be denied that suprarenal suppression might induce a similar picture.

Most of the fatalities following the use of the arsphenamins may be grouped under two heads—those referable to the liver and those affecting the brain and its membranes.

Kolmer and Lucke have shown that the arsphenamins in therapeutic dosage may induce slight structural changes in the liver and that huge

doses, such as are used to test the drug on animals, may cause quite considerable focal necroses. Warthin¹ says: "It is worthy of note that in a case of secondary syphilis dying of salvarsan poisoning focal necroses containing spirochaetes were present throughout the liver." In this connection the whole subject of jaundice in syphilis becomes pertinent for discussion. Without entering exhaustively into the subject it may be said that there are several types of jaundice observed in syphilis: (a) true syphilitic jaundice, appearing before any treatment has been begun and due doubtless to a diffuse degeneration of the liver cells produced by *Spirochaeta pallida*; (b) jaundice due to the combined effect of hepatic syphilis and arsenical treatment (in these cases the jaundice is a sort of Herxheimer reaction); and (c) jaundice due to structural changes in the liver induced by the arsenicals and going on in some cases to the development of acute yellow atrophy.

It is a significant fact that jaundice is much more commonly observed in syphilis now than before the introduction of arsphenamin. Osler found jaundice in syphilis (before arsphenamin) in 0.37 per cent. of cases. Harrison² found jaundice in 0.6 per cent. of cases of syphilis during or subsequent to arsenical treatment. Ravaut reports twenty cases of jaundice in patients receiving 94,672 injections of various arsphenamins. Scott and Pearson³ observed thirty-nine cases among 13,664 arsenical injections. Bailey and MacKay⁴ studied twenty-five cases of toxic jaundice developing in patients receiving arsenical and mercurial treatment. Silbergleit and Föckler⁵ report that they observed thirteen cases of acute yellow atrophy of the liver, all fatal, and all occurring in syphilitic patients who shortly before had been given mercurial and neo-arsphenamin treatment.

It can no longer be contested that jaundice and acute yellow atrophy are much more common nowadays than before the introduction of the arsphenamins. Nevertheless, we find a high incidence of such complications in certain countries and in the hands of certain clinicians and a low incidence elsewhere.

Is there any explanation for the discrepancy in the incidence of this complication? The writer believes that there is. In my own clinic in the Polyclinic Hospital (Graduate School of Medicine of the University of Pennsylvania) over 12,000 injections of the arsphenamins have been given, and we have only observed three cases of jaundice.

1. Warthin: Am. J. Syphilis **2**:445 (July) 1918.

2. Harrison: Quart. J. Med. **40**:321 (July) 1917.

3. Scott and Pearson: Am. J. Syphilis **3**:629 (Oct.) 1919.

4. Bailey, C. V., and MacKay, A.: Toxic Jaundice in Patients Under Anti-syphilitic Treatment, Arch. Int. Med. **25**:6286 (June) 1920.

5. Silbergleit and Föckler: Ztschr. f. klin. Med. **88**:333, 1919.

Furthermore, we have only encountered two mild cases of exfoliative dermatitis, a condition which is essentially an expression of arsenical intoxication.

What is the explanation of this low incidence of jaundice and exfoliative dermatitis? I believe it to be due to the fact that, for purposes of scientific investigation, our treatment of syphilis is an exclusive arsenical treatment. We are studying the effect of arsphenamin and neo-arsphenamin on syphilis, and we do not complicate this study by administering mercury. The arsenical treatment is fairly vigorous, patients receiving two 0.4 gm. doses of arsphenamin or two 0.9 gm. of neo-arsphenamin twice a week. Some patients have had this treatment continued until fifteen or twenty treatments have been given without interruption. We have never encountered a case of yellow atrophy of the liver or of encephalitis. In my private practice treatment has at times been much more intensive than that indicated above, and yet no hepatic, cerebral or cutaneous complications have occurred. I am of the opinion that conjoint mercurial and arsphenamin treatment, while perhaps more curative, is more liable to complications and fatalities. Some clinics in which mercury and arsphenamin are conjointly used encounter jaundice and dermatitis far more commonly than we do.

Wechselmann⁶ says: "My entire experience with more than 25,000 injections forces me to conclude that salvarsan is much less toxic than mercury. My department in which salvarsan is used almost exclusively has given me much less care and trouble during the past three years than in the previous period when mercury was employed."

A remarkable and unfortunate series of cases of "Delayed Arsenical Poisoning" is reported by Strathy, Smith and Hannah.⁷ They describe fifty-eight cases of late arsenical poisoning, eight of which were fatal, the symptoms developing, on an average, forty-three days after the last arsenical treatment. Jaundice was the most prominent symptom, being present in all of the fatal cases and in thirty-nine of the nonfatal group. There were also eight cases of exfoliative dermatitis. The writers state that "intensive treatment" was used, i. e., doses of arsphenamin and mercury, each once a week for seven or eight weeks. Intramuscular injections of mercurial oil (gray oil) were given at the same time as the arsenical treatment. Nearly all of the patients were treated with foreign makes of neo-arsphenamin. The patients were all between 20 and 40 years of age. Necropsy examinations in most

6. Wechselmann: *The Pathogenesis of Salvarsan Fatalities*, trans. 1913, St. Louis, p. 106.

7. Strathy, Smith and Hannah: *Lancet*, April 10, 1920, p. 802-807.

of the cases exhibited changes in the kidneys, in addition to hepatic atrophy. The greatest total amount of arsphenamin used in any case was less than 7 gm. and the least amount 2.2 gm. These cases in all probability represent arsenical poisoning due to the vigorous conjoint use of mercury and arsenic. The authors themselves suspected this for they say: "A few of the patients showed slight symptoms of mercurial poisoning, but mercury is known to be an irritant of the kidneys and in excessive doses to cause degeneration of the tubular epithelium, and it seems not at all unlikely that for this reason it acted as a predisposing factor.

The pathogeny of such poisonings is reasonably clear. Mercury in vigorous dosage, particularly when the insoluble salts are used, may severely irritate the kidneys and inhibit their power to eliminate arsphenamin. Within a short time after an injection of arsphenamin most of it disappears from the blood and is lodged in the organs, one of the chief reservoirs being the liver. If the eliminatory activity of the kidneys is impaired, it is obvious that the arsphenamin will remain for a longer time and in larger quantities in the liver, for which organ it has a considerable affinity. Too long a residence in the liver may cause the drug either to become oxidized with the production of arsenoxid, or the arsenical radical may become split off and produce the symptoms of arsenical poisoning.

The Salvarsan Committee, appointed by the British Medical Research Council, in its first report referred to some outbreaks of toxic jaundice, attended by a high fatality, which occurred in certain military hospitals after the use of the organic arsenicals. At the suggestion of the committee, Dr. H. M. Turnbull made an examination of the tissues from eight fatal cases. He concludes that "the liver in all cases was the site of a severe pathologic lesion, a lesion more severe than that in any other organs. . . . The liver was the seat of severe degeneration and necrosis.

"The kidney was available for examination in six cases, and in all showed a severe parenchymatous degeneration." No true nephritis was present. Turnbull regarded the kidney changes as secondary.

COMPARATIVE EFFECT OF ARSPHENAMIN AND NEO-ARSPHENAMIN

While the studies of Kolmer and Lucke indicate that similar structural changes occur after the use of arsphenamin and neo-arsphenamin, they call attention to the fact that the changes are distinctly less severe after neo-arsphenamin. This finding is in harmony with clinical observation. It may be definitely stated that neo-arsphenamin has less than one half the toxicity of arsphenamin and is unquestionably a safer remedy. This is due in part to the fact that one of

the anchoring groups—amino group—is closed, and furthermore, to the fact that neo-arsphenamin is neutral in reaction and does not in ordinary concentration produce hemolysis.

The studies under discussion indicate that the most damaging solutions of arsphenamin are acid solutions, an observation fully confirmed by the tragic results of inadvertently administered solutions of unneutralized arsphenamin in the human subject.

It is probable, however, that the vascular injuries described by Kolmer and Lucke are not solely due to solutions of strong hydrogen-ion (acid) concentration on the one hand nor to strong hydroxyl-ion (alkaline) concentration on the other, as similar although milder changes are observed after the use of neo-arsphenamin. It is possible that such changes are in considerable part arsenical in origin.

STRUCTURAL CHANGES INDUCED BY MERCURY

It has long been known that mercury has an affinity for the kidneys and that mercurial poisoning is apt to be associated with a nephritis. Accidental poisoning with mercuric chlorid kills in this manner.

The studies of Kolmer and Lucke are interesting in that they demonstrate that relatively short courses of mercury may produce perceptible renal changes. Even in rats that received treatment by mouth for from four to six weeks recognizable changes were observed in certain organs. These rats received 2 mg. (1/30 grain) of yellow mercurous iodid a day. This would correspond to 2 grains daily for a man weighing 130 pounds. This is somewhat larger than the ordinary therapeutic dose but not greater than the old method of administering an increasing number of pills daily until "some characteristic toxic effect of the drug is produced."

This dosage in rats caused slight structural changes in the spleen, liver and heart, but more pronounced alterations in the brain and kidneys. Remarkable to relate, a distinct perivascular cell infiltration was observed about the vessels of the brain. This was seen in all of the animals treated sufficiently long with mercury, no matter how administered, but was never observed in animals treated with arsphenamin. As far as we know, this observation of Kolmer and Lucke has not been hitherto recorded. In order to determine whether animals of a higher species will exhibit similar changes, experiments are now being carried out on monkeys.

The kidneys of rats receiving yellow mercurous iodid for from four to six weeks showed hyaline and granular casts in the collecting tubules. Vacuolated epithelial cells and cellular shrinkage were observed in the convoluted tubules, and there was mild connective tissue proliferation.

More pronounced kidney damage was seen in the animals receiving more vigorous treatment by inunction, intramuscular or intravenous treatment. The channel of introduction of the drug did not appear to be a determining factor, nor the form of mercury used. The structural alterations were proportional to the amount of the drug in terms of pure mercury absorbed into the blood stream.

GENERAL DISCUSSION

Both the arsphenamins and mercury administered in therapeutic doses bring about some structural alterations in organs. These are doubtless ordinarily repaired like the changes that take place in various acute infectious diseases. The chief organs affected by the arsphenamins are the liver, the suprarenals and the blood vessels. The effects of mercury, on the other hand, are seen dominantly in the kidneys and in the brain. The pathologic findings and clinical experience would alike persuade one to utter two cautions: In mercurial treatment watch the kidneys; in arsphenamin treatment watch the liver. To be sure, as stated by Milian, in early syphilis jaundice may indicate either hepatic syphilis or a Herxheimer reaction, and will respond to more vigorous treatment when the less intense treatment has failed. Later in the disease, however, and particularly after the vigorous use of the arsenicals, the development of jaundice should lead to a suspension of all specific treatment. The treatment of syphilis requires the repeated use of these drugs. When used with circumspection and good judgment harmful results may in large part be avoided. When used unskilfully, without proper examination of the patient and without knowledge of warning signals, unfortunate results may take place. The fact should be emphasized that the body tolerates much larger amounts of arsphenamin than mercury. One may, for instance, administer intravenously to a white rat, fifty times as much arsphenamin as mercury. More mercury cannot be administered because it has too great an affinity for body cells. The therapeutic dose of arsphenamin is infinitely more destructive to the spirochete of syphilis than the therapeutic dose of mercury. The spirochetes in a chancre can be destroyed in a few hours by an injection of arsphenamin; this accomplishment is impossible with a single injection of mercury. Fatalities have occurred both after arsphenamin and mercury. Those after the former are much more tragic and fear inspiring, for the relation between cause and effect is obvious. Many scores, if not hundreds, of deaths after mercury have likewise been reported in the literature, but they are ordinarily more apt to be slow and insidious and less likely to be incriminative of the therapeutic procedure employed.

In conclusion, the writer cannot refrain from expressing his opinion that vigorous mercurial treatment is often responsible for arsenical intoxication when arsphenamin and mercury are used at the same time. Large doses of both ought not to be employed synchronously. When the two are used jointly their respective dosages should be inversely proportional to each other. It would appear best to give the courses of mercury subsequent to that of arsenic.