Effects on Castrated Animals

It is difficult, if not impossible, to give a definite figure for the activity of testosterone on castrated mammals compared with that of androsterone. Not only are the ratios different for prostate and seminal vesicles, but the slopes of the dose-response curves for the two substances are so different that no ratio is significant unless the level of response at which the comparison is made is also stated. This applies also to other compounds (Parkes).[12] Further, differences in the technique of dissecting and weighing the organs render it difficult even to make the comparison at the same level of response in different laboratories. Tschopp[11] states that testosterone given alone is twenty times as active as androsterone on the seminal vesicles. Butenandt[10] finds a ratio of more than 10 to 1. Our own experiments, carried out on groups of five rats castrated at 40–50 grams and used a month later, ten daily injections being given, are summarized in the table. From these results testosterone seems to be about two and a half to five times as active as androsterone on the prostate, the activity varying with the level of response at which the comparison is made. On the seminal vesicles it is about ten times as active at the level of response at which comparison is possible. Tschopp's[11] results give much higher ratios than these. Testosterone also differs from androsterone in producing a more normal weight relation between prostate and seminal vesicles.[4 13]

As regards its activity per capon unit on rats, testosterone does not, in our experience, come up to expectations. Per capon unit it is little, if at all, more active on the prostate than androsterone, whereas testis extracts, per capon unit, are many times more active. In this connexion Laqueur's[6] statement that the activity of testosterone on rats is greatly enhanced by the simultaneous administration of an *x* substance, itself inactive, from testis tissue, is of the greatest interest. Ruzicka[14] has recently referred to experiments which seem to confirm this statement.

Methyl and Benzoyl Derivatives

The activity of two derivatives of testosterone has also been investigated: methyltestosterone[14] and testosterone benzoate.[15] The former is produced by the introduction of a methyl group in position 17. Similar treatment of the other compounds of the series increases their activity

Substance	Total Dose (mg.)	Weight of		Amount of Androsterone (mg.) required to give similar effect	
		Prostate (mg.)	Seminal Vesicles (mg.)	On the Prostate	On the Seminal Vesicles
Testosterone	0.6	33	10	3.25	6.0
	2.0	61	27	7.0	20.0
	4.0	96	47	10.0	—*
	6.0	136	84	15.0	—*
	8.0	156	99	—*	—*
Methyl-testosterone	2.0	75	32	9.0	20 +
—	Uninjected Controls	16	4	—	—

* Glands of this size not obtained in ten days with androsterone.

on rats considerably and their activity on capons slightly. Methyltestosterone proved to be appreciably more active on rats than testosterone (see table), but duplicate tests on capons showed that the activity was considerably less than that of testosterone—only about one-third. As a result, methyltestosterone, per capon unit, is much more active on rats than is testosterone. This is an anomalous result compared with those obtained on the other compounds, and there seems to be no obvious reason for the difference. The behaviour of the benzoate is also peculiar. Androsterone benzoate has a delayed and prolonged action on the capon comb as compared with androsterone, but the ultimate amount of growth produced by the benzoate is of the same order as that produced by a similar amount of free androsterone. The delay in effect due to benzoylation of androsterone is similar to that produced by benzoylating oestrone, but much more pronounced. Testosterone benzoate, however, even in comparatively "large" doses, has no immediate and little, if any, delayed effect on the capon comb. Thus 1 mg. given over five days to each of a group of five capons produced no detectable enlargement within four weeks. This comparative inactivity of testosterone benzoate is most unfortunate, because the possibility of obtaining a prolonged effect from a short series of injections is of great clinical interest.

We are much indebted to Professor Ruzicka and Messrs. Ciba for supplies of the substances referred to above.

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CHRONIC LEAD POISONING DUE TO THEATRICAL GREASE PAINT

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We report the following case to draw attention to the possibility of acquiring lead poisoning from the use of theatrical grease paint. This origin for lead poisoning has not previously been recorded so far as we have been able to ascertain. In the patient whose history is set out below, a distinguished actress playing the leading part in a London theatre, a very serious illness resulted from the use of grease paint containing large quantities of lead. The consequences of this illness were disastrous to the patient. She became gravely ill, lost her work, narrowly escaped an abdominal operation, and only began to improve after blood transfusion. Step by step evidence was collected to prove that this was a case of lead poisoning, and finally we were able, by a series of chemical analyses, to trace the poison to its source.

We are informed that grease paint similar to that used by our patient has been offered for sale extensively both in London and the provinces. If this continues other cases of lead poisoning similar to this are likely to occur, as well as much vague ill-health of a less clearly defined nature.

History of Case

The patient was an actress aged 28 years. On January 5th, 1936, she consulted one of us (E. L. B.), saying that she had not felt well for the past four weeks, her symptoms being:

1. Tiredness and breathlessness after a little physical or mental strain.
2. Anorexia.
3. Indigestion and flatulence.
4. Menorrhagia.
5. Metrorrhagia.

On account of these uterine symptoms she was taken to see a consulting gynaecologist, who examined her thoroughly but could find no pathological condition in the pelvis. He suggested her symptoms might be due to anaemia, and advised a blood count. The blood count (carried out by C. D. on January 6th) showed the typical blood picture of lead poisoning. The actual figures were: haemoglobin, 70 per cent. ; red blood cells, 3,500,000 per c.mm. ; colour index, 1 ; leucocytes, 8,000 per c.mm. ; differential count—polymorphs, 68 per cent. ; lymphocytes, 28 per cent. ; monocytes, 3 per cent. ; eosinophils, 1 per cent. A great many stippled red cells were seen in stained films, and there was a moderate degree of polychromasia. There was also a slight degree of poikilocytosis and anisocytosis.

Five days later, when the patient was seen again, she complained of:

1. Waking up in the night with acute colicky pains in the lower part of the abdomen, relieved only by firm pressure on the affected part.
2. Frequent vomiting, especially after food.
3. Anorexia.
4. Indigestion and flatulence.
5. Severe neuralgic pains over the left shoulder.
6. Persistent headache.

The patient looked pale, anxious, and anaemic. Her eyes were sunken, and she pressed on her abdomen continually to alleviate her pain. Her temperature was subnormal. The pulse was slow and feeble, but regular in time and force. Her respirations were 20 per minute. The tongue was furred, there was no blue line round the gums, and the teeth were in good condition.

The abdomen was retracted, moving regularly with respiration, and on light palpation was tender all over, especially the lower part. There was no rigidity of the abdominal muscles. There was no tenderness per rectum or any abnormal swelling felt in the lateral fornices.

The central nervous system was normal. Nothing abnormal was noticed in the chest. The blood pressure was 120 systolic and 71 diastolic. The urine contained no albumin or sugar, and the specific gravity was 1020.

A diagnosis of chronic lead poisoning was made on the evidence of the clinical symptoms and blood picture. The patient was advised to leave her house (which was then being painted) and go to a nursing home, where treatment could be undertaken. However, she insisted on playing at the theatre that evening, but after the play was taken to Brighton by her husband.

On January 12th, whilst staying at Brighton, the patient complained again of acute abdominal pain and vomiting, and sent for Dr. Kendall Price, who kindly supplied the following notes. " Patient looked very ill, pale, and anaemic, and in great pain ; temperature 99°, pulse 92, tongue furred, no blue line round gums, teeth good. Chest, nothing abnormal ; abdomen, tender and slightly rigid in the left iliac fossa ; spine normal ; C.N.S., normal ; urine, clear ; no albumin ; no sugar."

On January 13th the pain in the abdomen was worse and very little relief was obtained from morphine. A blood count on January 14th by Dr. Janes revealed: haemoglobin, 68 per cent. ; red blood cells, 3,100,000 ; colour index, 1.1 ; leucocytes, 12,000 ; differential count—polymorphs, 81 per cent. ; lymphocytes, 12 per cent. ; monocytes, 7 per cent. ; polychromasia +; punctate basophilia + +; normoblasts numerous. Two days later a specimen of urine was examined, and this showed 0.71 mg. of lead per litre of urine (Roche Lynch method).

The diagnosis was now clearly established, and the course for treatment was plain. Unfortunately, however, the patient did not make any immediate response to iron therapy. In fact further blood counts showed a slight increase in the anaemia.

In view of the fact that the haemopoietic system was not responding to the iron and other treatment the patient was given a blood transfusion of 300 c.cm. of citrated blood from a Group 4 Red Cross donor on February 11th. There was no reaction from the transfusion. Since the transfusion the patient's health has steadily improved, and by the end of February she felt well enough to consider resuming some of her professional engagements.

The anaemia is now disappearing, as shown by the following tests.

February 19th: haemoglobin, 82 per cent. ; red blood cells, 3,840,000 per c.mm. ; colour index, 1.1 ; leucocytes, 9,000. No stippled red cells found. March 3rd: haemoglobin, 93 per cent. ; red blood cells, 4,600,000 per c.mm. ; colour index, 1 ; leucocytes, 9,000 per c.mm. There was no polychromasia, and no stippled red cells were seen.

As soon as we were convinced that this was a case of lead poisoning we began a search for the manner of " infection." We submitted samples of water for analysis with completely negative results. We examined the house into which the patient had been moved, but could find no clue to the source of the illness. We made a careful inquiry into the possibility of contraceptives, but there had been no exposure to " infection " from such a source. Finally, on January 26th, Dr. Price brought to Dr. Janes a sample of grease paint which the patient had been using, and this was found to contain lead. The sample was sent to Messrs. Woodcock and Mellersh, who reported that the grease paint contained 39.27 per cent. of lead, equivalent to lead oxide 42.32 per cent. The lead appeared to be present in the form of lead oxide, chiefly the monoxide.

This completed the story, which may be briefly summarized in the following sentences.

A young actress developed the classical symptoms of lead poisoning. Blood examination revealed anaemia and stippled red cells. The diagnosis was confirmed by the finding of large quantities of lead in the urine and faeces. The source of the lead poisoning was traced to the use of a grease paint containing approximately 40 per cent. of lead.

The Diagnosis of Lead Poisoning

In this case the diagnosis of lead poisoning was suggested first as the result of a consideration of the clinical condition and blood picture. The essential features of the blood picture were anaemia combined with a great increase in stippled red cells. Later very convincing confirmatory evidence was provided by the chemical analysis of urine and faeces, which showed that the patient was excreting large quantities of lead, but the diagnosis was founded on the clinical history and blood tests. We draw attention to this point because in recent years increasing emphasis has been placed upon the estimation of lead in the urine and faeces as specific evidence for the confirmation or exclusion of lead as a factor in suspected cases of lead poisoning.[1] The growing reliance on analytical procedures for the recognition of lead poisoning calls for a clear recognition of the serviceability as well as the limitations of these measures.

Traces of lead may be found in the urine of healthy people. This is due to the fact that small quantities of lead are ingested with such food as sausages, meat, beans, cherries, and other fruit. It appears from the observations of Kehoe and his colleagues that the average American may ingest from one-fifth to one-third of a milligram of lead per diem, and excretes from 0.02 to 0.08 mg. of lead per litre of urine and from 0.03 to 0.1 mg. per gram ash of faeces.[2] Similar figures have been published for other countries. Thus Francis showed that the average rate of excretion of lead for Londoners was 0.049 mg. per litre and for country people 0.023 mg. In Australia also Badham and Taylor found an average lead excretion of 0.02 mg. for healthy people.[3]

This being so it is obviously unsafe to base a diagnosis of lead poisoning on the discovery of lead in the urine

unless this is estimated quantitatively and found to be far above the normal limits. Actually in lead poisoning the patient usually excretes at least 0.1 to 0.3 mg. of lead per litre,[4] and when figures such as this are reached there is strong evidence for lead poisoning. In our patient the quantity of lead excreted was more than ten times the normal, so that the test provided very valuable confirmatory evidence. However, in view of the pitfalls that may beset diagnosis by urine tests, it is important to recollect the paramount importance of the clinical history and blood picture.

The stippled red blood cell is easily recognized in a Leishman-stained film. The affected cells have blue granules, which may be fine and numerous or large and scanty. Whitby and Britton have shown that the stippled cell is really a young red blood cell (reticulocyte), in which the basophilic material has been slightly altered by lead,[5] Anaemia in association with a high stippled red cell count should always suggest lead poisoning. The two conditions in which the blood picture mostly resembles lead poisoning are acholuric jaundice and chronic malaria, in both of which the reticulocyte count is commonly higher than normal. These were each excluded in our patient.

Susceptibility to Lead

It is well known that there is a great variability in susceptibility to lead poisoning. Figures in the pottery industry seem to show that women are about twice as susceptible as men, but this may be due either to the relatively greater dangers in the processes in which women predominate or to their average shorter duration of employment. The records of plumbism show that two-fifths of all reported cases occur during the first eighteen months of employment.[6]

The grease paint used by our patient was the same brand as that used by several other actresses, but so far as we know no other case of lead poisoning occurred. We had the opportunity of examining eleven other members of the cast, and made a special search for stippled red cells in blood films, but these tests were all negative. It is possible that they might have developed symptoms if the use of this grease paint had been continued, but, naturally, this particular brand was not used so freely when it became known that the illness of the chief lady was attributed to this agent. Our tests on other members of the cast were carried out some three or four weeks after this became common knowledge in the company. There was, however, a good deal of ill-health, and there were many complaints of tiredness and headaches among those who had used this grease paint previously.

Composition of Grease Paint

Grease paints consist of various pigments mixed usually with a white base and with fats and waxes. They are sold in many different shades of colour, and should, like lipstick, be "proof against osculation."

The most useful pigments for grease paint are the "earth pigments," which owe their colours to the presence in them of oxide of iron or iron and manganese. The presence of anhydrous ferric oxide colours an earth red, hydrated ferric oxide colours it yellow, whilst oxides of manganese colour it brown. These natural pigments are perfectly harmless, and they alone provide the means for obtaining a number of useful shades. By a judicious mixture with other innocuous materials, such as carmine, alizarin, crimson lake, ultramarine, and lamp black, it is possible to obtain the bulk at any rate of the requisite shades.[7]

The white base is used to provide the necessary opacity for a white paint or to tone down other colours. Zinc oxide alone is often used, or this may be mixed with mineral ingredients which enter into the composition of face powders, such as precipitated chalk, kaolin, and talc.

The function of the fat base is to make the paint sufficiently hard to form a firm crayon. The mixture of fats and waxes must have a melting point above the normal temperature of the blood, and also be sufficiently soft to render the application of the paint easy. The following ingredients are usually employed—vegetable oil and fat such as lard, suet, tallow, etc., animal waxes such as beeswax, spermaceti, and lanolin, mineral oils and waxes such as liquid, hard, and soft paraffin or ceresin.

The paint used by our patient was of a carmine shade, labelled C2. The chemical analysis already quoted found it to contain almost 40 per cent. of lead. This was present in the form of a lead oxide or litharge (PbO). It was at first thought that the lead might be in the form of red lead, but this could not be detected by the peroxide test.

The analytical chemists suggested that the makers of this grease paint had incorporated some ordinary vermilionette containing litharge coloured with eosin. If this were the case the fatty material of the grease paint would be an additional source of danger, as the litharge would tend to combine with the fatty acid forming the lead soap.

We purchased a number of other samples of grease paint from the same source and submitted these to Messrs. Woodcock and Mellersh for analysis. None of these contained so much lead as the original sample, but one contained 9 per cent. of lead, another approximately 6 per cent., and another 1 per cent. Three samples of lipstick and one sample of "grease remover" supplied by the same firm were found to be free from lead. We have not been able to discover any further details of the manufacture of these lead-containing grease paints, but we suspect that the makers purchase the pigments from various sources, and may be unaware that they contain any dangerous constituents.

Incidence of Lead Poisoning

There has been a steady decrease in the incidence of lead poisoning in this country during the last thirty years. The notified cases in 1900 were 1,058; in 1910, 505; in 1920, 289; in 1930, 265. During the year 1934, 198 cases were notified, chiefly amongst workers in painting, pottery, shipbreaking, and smelting of metals.[8] So far as we have been able to ascertain no previous case of lead poisoning due to grease paints has been reported in this country.

Summary

This paper records a serious case of chronic lead poisoning in an actress. The diagnosis was based on the clinical history and typical blood picture. It was confirmed by the finding of large quantities of lead in the urine and faeces. The source of the poisoning was traced to theatrical grease paint, which we find frequently contains large quantities of lead. We anticipate that other serious cases of lead poisoning and much minor ill-health are likely to follow the use of a cosmetic containing such dangerous constituents.

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