2. It seems possible that the therapeutic effects of streptomycin are due to bactericidal rather than to bacteriostatic action. This is certainly so when high concentrations are attained locally, as in the treatment of infections of the urinary tract.

The streptomycin used in this work (streptomycin hydrochloride Merck) was supplied for studies in this hospital by the Streptomycin (Non-tuberculous Conditions) Clinical Trials Committee of the Medical Research Council, to whom I express my thanks. I am indebted for valuable technical assistance to Miss P. M. Waterworth.

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CALCIFEROL IN THE TREATMENT OF CUTANEOUS TUBERCULOSIS

BY

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The value of calciferol in the treatment of lupus vulgaris is now generally known. Its mode of action is still a matter for speculation, and is likely to remain so until more serial observations upon cases undergoing this treatment have been made. This report describes a series of such cases treated at Charing Cross Hospital.

The advantage of calciferol over previous methods, with the results of which it seems to compare most favourably, is almost as much a social and economic as a medical one. That a large number of man-hours are saved by patients taking a drug by mouth rather than attending a department for heliotherapy, etc., for many hours a week is obvious. In the present need for maximum effort and full employment this is a factor of considerable importance, and does not seem to have been sufficiently stressed.

This method of treatment seems to have started on both sides of the Channel at about the same time, and similar results were reached quite independently, which seems to us to add great value to these conclusions. Charpy (1943), in France, Fanielle, in Belgium, and Dowling and Prosser Thomas (1946), in London, appear to share the honours of being the pioneers in this treatment.

For the sake of brevity the cases are reported in tabular form, and those of special interest are referred to separately

Details of Cases

Case No.	Sex	Age	Duration of Lesion	Class of Lesion	Site of Lesion	Treatment	Result
1	F	5	3 mths.	A	Malar	1	a
2	F	43	25 years	A	"	1	c
3	M	34	30 "	B	L. hip	1, 2	a
4	F	31	6 "	A	Malar	1	a
5	F	62	20 "	A	Face	1, 2	b
6	F	46	28 "	A	Malar	1	a
7	M	26	11 "	A	Neck	1	a
8	F	56	3 "	A	Both legs	1, 2	b
9	F	68	20 "	C	Face	1	c
10	F	71	50 "	B	Face, neck	1	a
11	F	59	25 "	Scrofuloderma	Neck	1	b
12	F	20	4 "	Miliaris faciei	Face	1, 2	d
						U.V.L.	

Key to Table

Class of Lesion (the Typical Nodules were of course Present in All Cases)

- A. Lesions less than 4 in. (10 cm.) in diameter. No deformity produced by scarring.
 B. Lesion greater than 4 in. in diameter; scarring may be extensive but no disabling deformities present.
 C. A severe lesion producing extensive scarring and disabling deformities—e.g., ectropion or destruction of nasal cartilages.

Treatment Groups

1. Calciferol 50,000 units with added calcium thrice daily ("high potency ostelin" tablets).
 2. Calciferol, either in pure alcoholic solution or in oily solution ("sterogyl"), 600,000 units per ml. twice weekly.

Result Groups

- (a) Lesion clinically healed.
 (b) Lesion very much improved, but one or two possible foci of activity still remaining.
 (c) Progress of lesion arrested; "minimal favourable response."
 (d) No apparent response; lesion continuing to progress.

Discussion of Results

The twelve cases reported (see Table) have been under treatment for nine months or longer. Six were cured, three were very much improved, two have shown very little improvement, while one has shown no response to treatment.

These figures may be compared with the results obtained by Dowling and Prosser Thomas (1946) up to December, 1945—18 cured, 9 much improved, and 5 somewhat improved—also with those of Kuske (1946) at Berne—50% excellent, 20% arrest of lesion, and in the remainder a "minimal favourable response." (The assumption that this last group corresponds to result group "c" in our table of results is our own.) Two other series which give figures for results are those of Dowling, Macrae, and Jones (1946) with 20 cases and 14 (70%) recoveries, and of Dr. Emrys Jones, of Cardiff, who had 18 cases with 16 "cleared" (89%).

Thus in some 82 cases we find 54 (66%) which have healed under the influence of calciferol, and it is probable that with further treatment this figure will be higher still. It must, however, be remembered that the Finsen Institute in Denmark claimed 735 cures out of 975 cases (75%) between 1914 and 1923 using methods other than the administration of large doses of calciferol.

It is probably safe to assume that about 60% of cases of lupus vulgaris in this country at this time may be cured by calciferol therapy alone (the reason for qualifying this statement is discussed on p. 388). It is of interest to note that streptomycin has been tried out in America on cases with lupus vulgaris, but the results have so far not been as successful as with calciferol.

Two Cases of Special Interest

Case 10.—This patient complained of flatulence, sickness, and diarrhoea after taking one "ostelin" tablet thrice daily for 14 days. She was told to continue with the tablets unless the symptoms got worse, when she was to stop taking them and report to

us. She returned two weeks later, having stopped the tablets for a week. She complained of some frequency of micturition. Her urine was found to be normal but perhaps increased in amount. A plain radiograph of the abdomen revealed fusion of L3 and L4, with calcified mesenteric glands probably of tuberculous origin; also possibly, in view of the history, a large amount of calcium in the colon. The patient continued without calciferol and was examined two weeks later. Her symptoms were then quite relieved. A plain radiograph appeared the same as before. Barium was given by mouth, and later the patient was examined under the x-ray screen, when it was obvious that the calcium deposits were not in the caecum or colon but only in the mesenteric glands. More intensive questioning revealed that there was some suggestion of a tuberculous kidney 30 to 40 years ago because of backache then, but it had not been very thoroughly investigated and there was nothing else that the patient could recall.

This case is reported in detail because we have already been warned of the possibility of "flaring up a lesion" with calciferol (Dowling and Prosser Thomas, 1946; Dowling, Macrae, and Jones, 1946). In this case there may have been a quiescent tuberculosis of the mesenteric glands, which seem so well calcified now but which the calciferol may have temporarily stimulated. It is therefore important before starting treatment to consider the possibility of an exacerbation not only of the skin lesion but of a lesion elsewhere.

Case 12.—This was a resistant case of lupus miliaris faciei. (Another case of lupus miliaris faciei has been treated by us with calciferol, but was not under observation long enough to qualify for the table of case results.) The patient presented with symmetrical aggregations of lupus nodules on forehead, cheeks, chin, and neck. There was no family history of tuberculous diseases, and thorough investigation revealed no evidence of tuberculosis elsewhere. One "ostelin" tablet thrice daily (150,000 units of calciferol daily) resulted only in intense thirst and troublesome borborygmi: no effect was observed on the lupus lesions. After two weeks' rest the course was restarted, but again symptoms of intolerance caused us to stop it.

We then tried the effect of calciferol locally. An ointment was made up with "radiostol" in a base of paraff. molle to give a concentration of approximately 70 units of calciferol per gramme. This was applied to the lesions and rubbed well in twice daily. Within three weeks there was a most dramatic improvement in the lesions: the erythema faded and the papular eruption almost faded. A stronger ointment was therefore tried, using pure calciferol in alcoholic solution in the same base at a concentration of 150,000 units per gramme. After two weeks' use of this ointment the condition had relapsed to its original state. This may well have been a flare-up caused by the very high local concentration of calciferol, or the alcohol solution may not have been absorbed through the skin. A return to the "radiostol" ointment now had no effect, nor did the oral administration of pure calciferol in doses of 300,000 units twice weekly.

An ointment corresponding to the stronger of the above was then made up, substituting A.T.10 (dehydrotachysterol) for the calciferol (0.375 mg. per g.); the patient applied this to the left half of her face and the calciferol ointment to the right half for four weeks. Neither appeared to affect the lesions. She has completed a course of ultra-violet irradiation, but her face remained in much the same state when last seen.

Methods of Administration

Ostelin High-potency Tablets.—Each tablet contains 50,000 units of calciferol with added calcium. The usual dose is three tablets a day for 14 days when the patient starts treatment. The blood chemistry is investigated beforehand (see below). When the patient is seen in 14 days the blood chemistry is again investigated and the dose is maintained if there are no untoward symptoms. After a further 14 days the patient is seen again and, if no toxic symptoms have developed, carries on with the same dose for a month. A further specimen of the blood is then

taken, and if all is well the patient comes up once a month for observation. If toxic symptoms develop either the calciferol is withheld or the dose is reduced for a week or two. After about four months the patient is usually given a rest from calciferol for two to eight weeks. This method is based on the original method used by Dowling and Prosser Thomas (1946) in 1943.

Pure Calciferol in Alcoholic Solution (5 mg. per ml.: 1 mg. corresponds to 40,000 units of activity).—We diluted this to an emulsion with 1 fl. oz. (28 ml.) of water, and the patient took it in three doses during the week. This corresponds to the solution in propylene glycol used by Charpy (1943), the administration of which, combined with the giving of calcium (as calcium gluconate) or 1 to 2 litres of milk a day for one or two months, is becoming known on the Continent as the "méthode de Charpy."

Sterogyl calciferol—600,000 units in ampoules for oral or intramuscular use. We did not give any by injection to these cases.

Radiostol, employed to make up the ointment for Case 12.

Toxic Effects

At some stage of treatment most of our cases showed symptoms attributable to the large doses of calciferol. These were: salty taste in the mouth, thirst, anorexia, nausea, vomiting, flatulence, abdominal pains, diarrhoea, giddiness, lassitude, and frequency of micturition. Case 8 complained of headaches and cramps in the legs.

It was most noticeable that the symptoms occurred almost entirely when the patients were taking ostelin tablets. Furthermore, we found that two cases developed severe symptoms with ostelin tablets but were unaffected by the pure vitamin (started six weeks after the last course of ostelin) in dosages of 1,200,000 units weekly for three weeks. Cases 3 and 7 had no toxic symptoms at any time. All cases which showed symptoms apart from a salty taste in the mouth or thirst had chest and plain abdominal radiographs taken. Only in Case 10 was any abnormality found.

Case 8 was carefully investigated for hypertension or peripheral vascular failure. There was some tenderness of the calf muscles, but the circulation of the feet was always good and x-ray examination of the legs showed no evidence of calcified arteries. Blood pressure was normal.

Comparison of Intolerance of Calciferol and A.T.10

A.T.10 is probably the best substance to use as a control in calciferol investigations. A synthetic compound resembling tachysterol (the precursor to calciferol in the ergosterol-calciferol synthesis), it has the same effects upon the blood chemistry but does not cure rickets. We are grateful to Dr. Nathan for a gift of A.T.10 produced by Bayer (Darmstadt), which was used as our control.

A healthy man aged 24 was given a course of pure calciferol for eight days. When the blood chemistry had been normal for one week after this a similar course of A.T.10 was given, the symptoms being noted as they occurred. On neither occasion was calcium added. Intense thirst developed on the fifth day of taking calciferol and on the fourth day when taking A.T.10; anorexia developed on the seventh day with both substances, and marked borborygmi were noticed a few hours later. Also at this time there developed a definite "sensitivity," hardly amounting to pain, over the whole abdomen on palpation. This suggests that the above symptoms are not specific for calciferol in high doses but follow some effect of calciferol which is also produced by A.T.10.

Experience suggests that it is intensified by giving additional calcium. It has, however, been previously recorded that these symptoms bear no definite relation to the serum calcium (Dowling and Prosser Thomas, 1946), an observation which we can confirm.

Blood Chemistry

The reactions of the following factors in the patients' blood to dosage with calciferol were investigated: (1) the serum calcium; (2) the serum alkaline phosphatase; (3) the serum cholesterol. The serum calcium was estimated on each sample of blood before the other tests, and these were then done in the above order. (Our debt to Dr. Patterson, of the Institute of Pathology, and to his assistants for performing nearly 200 estimations is such that we feel compelled to acknowledge it in the text, where we hope it is less likely to be overlooked.) These are first done before any calciferol is given.

Serum Calcium.—Our results agree with those of others. After an initial lag of a few days up to two to three months the serum calcium rose in all cases, usually to about 11 mg. per 100 ml. (normal 9–11 mg.). At this level there were usually no symptoms except for some thirst. In some cases it rose to over 14 mg., and in one case to 15.2 mg. These higher levels were nearly always associated with symptoms of a fairly severe nature, but, apart from these cases, we did not notice any definite relation between the severity of the symptoms and the serum calcium level. However, we are of the opinion that a steady rise in the serum calcium is an indication for a reduction in the dose of calciferol if not for its complete withdrawal. All our observations have been on the total serum calcium levels. There is need for further research on the effects of the different forms in which calcium is present in the blood.

Serum Alkaline Phosphatase.—(Our results are given in King-Armstrong units, the normal values being 3 to 13 units.) Before starting treatment with calciferol the normal alkaline phosphatase in all our cases of lupus vulgaris was between 5 and 8.5 units. With the administration of calciferol there was sometimes an almost immediate fall in this figure, which then continued more slowly while the dose was maintained. In some cases it rose again while the patient was still on calciferol. When the reading became less than 4.5 there were nearly always some signs of intolerance. These symptoms, however, did not always disappear when the alkaline phosphatase rose again. Although inconclusive, it is interesting to note that at times there seemed to be some relation between the intensity of the fibrous reaction to the lesion and the relative value of the alkaline phosphatase. Although within normal limits it appeared that the better the fibrous reaction and the more scar tissue in the lesion the lower was the original reading. Thus in a case with few nodules of activity and a firm scar a reading of 4.8 units was found. A case showing more activity gave the figure of 8.2 units. As this finding seemed fairly constant it was suggested that a lesion showing chronic inflammation with a minimum of scarring would give a high figure: some weeks later the case with a lymphocytoma was seen, and the reading here was 14.7 (later readings have been 10 units and over). Finally, it was noticed that the serum alkaline phosphatase reacted on the whole much more rapidly to the administration of calciferol than the serum calcium. Experiments with a control subject showed a fall in the alkaline phosphatase to have started within one hour of taking 100,000 units of calciferol by mouth.

Serum Cholesterol.—It has been stated (Eichelberger and McCluskey, 1927) that in a case of tuberculous infection in which the resistance is good the serum cholesterol is nearly always raised above normal, and that if it returns to normal under treatment the prognosis is favourable. Conversely, in severe infections where the resistance is not so good the cholesterol level is low and the prognosis poor. The method used by Dr. Patterson for estimating serum cholesterol gives a reading in normal individuals of 140 to 240 mg. per 100 ml. Cases of lupus vulgaris all showed a relatively good resistance, and our initial figures were all greater than the normal. Two cases were over 300 mg. With calciferol the figures tended to rise at first, in some cases to 360 mg. or more. But with continuing treatment they began to fall towards normal. All these cases showed recovery or marked improvement. It was as a check on these figures that a case of bronchopneumonic phthisis was investigated. Before treatment (the patient came from the casualty ward and was severely ill) his serum cholesterol was

only 92 mg. per 100 ml. After three months' rest and intensive treatment with calciferol by mouth the figure had risen to normal (184 mg.) and he was able to go to a sanatorium. Our findings would therefore seem to confirm the above statement. There appeared to be a definite relation between the value of the serum cholesterol and the administration of calciferol in lupus vulgaris, and this relation follows the clinical course of the disease.

We should mention here the thorough investigation of the effect of calciferol on the blood sedimentation rate by Dr. Feeny (1946), at the London Hospital; he found that it is not constantly affected.

Discussion of the Effects of Calciferol

There are two ways in which calciferol may exert its effect.

1. *By Direct Inhibition of the Tubercle Bacillus.*—The only apparently serious suggestion that this may be the mechanism is contained in an unsupported statement by Bicknell (1946). So significant a finding would no doubt have been supported by the fullest evidence if this had been available. Nevertheless it is important that the effect should be investigated. We are grateful to Dr. Walker for permission to quote an experiment undertaken by him at the Glaxo Laboratories in which cultures of *Mycobacterium tuberculosis* were grown on media containing increasing concentrations of calciferol. There was no inhibition of the growth in concentrations approaching those *in vivo*. To investigate the possible effect upon the resistant "envelope" of the organisms cultures of fresh pathogenic tubercle bacilli were incubated for 24 hours with fresh human serum, and calciferol in various concentrations, in the Bacteriological Laboratory of Charing Cross Hospital. The "envelopes" were morphologically unaltered, and the organisms retained their vitality and pathogenicity up to a concentration of 500 units of calciferol per ml., where the serial concentrations were discontinued. It would appear, therefore, that calciferol has no specific effect on *M. tuberculosis*.

2. *By Increasing the Body Resistance.*—It is more probable that this is the effect of calciferol. In favourable cases the rate of tissue repair exceeds that of tissue destruction. The relatively raised alkaline phosphatase sometimes seen at the start of treatment may be an expression of a relative tissue lack of calciferol to meet the demands of local inflammation and repair. When repair and fibrosis become pathologically overactive we find a tendency to depression of the serum alkaline phosphatase. This was found in cases of scleroderma (Medvei, 1945) provided there was no element of hyperparathyroidism (Wigley and Hunter, 1945).

Earlier in this article the average recovery figures were qualified by the statement "in this country at this time." This refers to the variation of calciferol in the average diet of the population at different times—a factor already noted by Jaeger (1946) at Lausanne.

Effects of Calciferol on Some Other Diseases

1. *Other Tuberculous Diseases.*—(a) *Cerebral Tuberculomata* (2 cases):—No apparent effect. (b) *Tuberculous Meningitis* (2 cases, both fatal):—During the terminal stages the effect of giving calciferol intrathecally was investigated—in one case it was apparently well tolerated, but in the other it caused a reaction. (c) *Bronchopneumonic Phthisis* (1 case, quoted above):—Clinical and radiological improvement in three months.

2. *Skin Diseases.*—(a) *Pemphigus Vulgaris*:—A case of some years' duration in a woman of 53. At start of treatment with ostelin tablets there were several blisters, ulceration of the throat, cough and dysphagia. After 14 days she felt better and the blisters were fewer, so the tablets were increased from two to three a day. This was continued for two months, during

which time the blisters varied in size and number, although the patient felt well all the time. Then thirst developed and a rest of two weeks was given, during which time the blisters got worse. Calciferol was resumed, one tablet twice daily for three months with a month's rest between courses. Her present condition is good, with few blisters, and she feels much better. (b) *Lymphocytoma*:—This occurred in a woman aged 55. Biopsy showed dense aggregations of lymphocytes with very little fibrosis; there was a history of its having been present for one year. The Wassermann reaction was negative. This lesion improved under x-ray treatment, but when a fresh lesion appeared calciferol was tried—ostelin one tablet twice daily. With x-ray treatment the previous lesion was considered healed after six courses over two years. The fresh lesion was healed clinically with calciferol in four months. A further biopsy now showed a reversal of the histological picture, with dense fibrosis, dilated capillaries, and small discrete foci of lymphocytes. "Apparently a remnant of a pre-existing lymphocytoma" (Dr. Muende, St. John's Hospital, Leicester Square). (c) *Granuloma Annulare*:—One case, that of a woman aged 33. Calciferol had no effect on this lesion in any dosage orally or by local inunction.

3. A case of *multiple myelomatosis* improved while on calciferol.

Summary

Twelve cases of cutaneous tuberculosis are presented and the results discussed. Four methods of administration are outlined and some toxic symptoms described.

The effects of calciferol on blood chemistry were found to be as follows:—(a) a rise in the serum calcium usually occurs after prolonged administration; (b) an almost constant fall in the serum alkaline phosphatase generally occurs soon after the calciferol is given; and (c) the usually slightly raised serum cholesterol tends to increase before returning to normal.

The effect of calciferol appears to be that of increasing the body's resistance, and it does not seem to have any direct toxic effect on the tubercle bacillus.

Brief notes are given on some other diseases treated with calciferol.

We wish to thank members of the honorary medical staff, especially Dr. H. A. Dunlop, for valuable suggestions and advice and for permission to investigate the effect of calciferol on some of their patients; and Mr. Whittet, late chief pharmacist at Charing Cross Hospital, now at University College Hospital, for preparing the calciferol in various ways. We are also greatly indebted to Dr. Walker, of Glaxo Laboratories, for supplies of pure crystalline calciferol in nitrogen-sealed ampoules for these investigations and for undertaking the assay of the (oily) solution of A.T.10.

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Preventive Medicine and Public Health, by Prof. Wilson G. Smillie (New York, the Macmillan Company, 30s.), is an interesting book intended for the medical student who expects to practise medicine in the community. The greater part of most textbooks of public health are on environmental hygiene and the communicable diseases. Nearly half this is on child hygiene, adult health protection and promotion, and public-health administration, much of this last section being devoted to health education, medical social work, and allied subjects. The part on adult health protection will break new ground to many readers; it includes sections on geriatrics, the preventive aspects of peptic ulcer, appendicitis, heart disease, obesity, diabetes, arthritis, allergy, and alcoholism. Treatment as well as prevention is discussed in some of these sections. British readers will find much food for thought in all parts of the book—for instance, the table showing positive Wassermann reactions found in a variety of economic and social groups giving rates per thousand varying from 1 in university students, 8 in prospective blood donors, and 12 in premarital tests, up to 110 in street beggars, 240 in convicts, and 300–700 in prostitutes; the psychological implications are obvious. The diagrams are most instructive.

RETROPERITONEAL HAEMORRHAGE IN PREGNANCY

BY

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The following case may be of interest because of the great rarity of retroperitoneal haemorrhage complicating pregnancy (six cases have previously been reported), and because of its association with a condition of eclampsia and a concealed accidental haemorrhage.

Case History

The patient was a 2-gravida, aged 25, whose general health was good. She had had scarlet fever at the age of 16. In September, 1945, she had a normal pregnancy—labour of 36 hours' duration terminating in the spontaneous breech delivery of a male child weighing 8 lb. (3.6 kg.) which died from cerebral haemorrhage after half an hour.

Her menstrual history showed menarche at 14; periods regular, 28-day cycle; normal loss; no dysmenorrhoea; no intermenstrual discharge. Her last menstrual period began on Aug. 11, 1946, and the expected date of confinement was May 18, 1947. The patient had made regular attendances at her antenatal clinic. Her last visit was on April 3, when the uterus was found to be of the size of 34 weeks. The position was vertex R.O.A., the head not engaged; the foetal heart was heard. She was admitted as an emergency case at 3.30 p.m. on April 10.

At 3 p.m. that day she had felt weak and sick and had suddenly collapsed with sharp pain in the hypogastrium. She was reported to have had one fit at home and two fits while in the ambulance en route to the hospital. Pain was severe and constant. There was no history of a "show," and she had not had any frequency of micturition or dysuria. The rectum had been evacuated in the morning.

On examination she was pale and restless. The pulse varied between 110 and 120, and was of very poor volume. The blood pressure was 70/45. Nothing abnormal was detected in the heart, and the lungs were clear. The uterus was of 36 weeks' size; the position of the foetus was difficult to detect, but was thought to be vertex R.O.A. The foetal heart could not be heard. The uterus was tense, tender, and ligneous. There was no loss per vaginam. A catheter specimen of urine revealed albumin (Esbach's reaction, 10 parts per 1,000). The haemoglobin was 50%. A provisional diagnosis of concealed accidental haemorrhage and antepartum eclampsia was made.

In view of the condition of the uterus and the state of profound shock a conservative attitude was adopted and anti-shock therapy was immediately instituted. Morphine, 1/4 gr. (16 mg.), was given immediately and again four hours later. A blood transfusion of group O cross-matched blood was begun, and the patient was put on to a half-hourly pulse chart, four-hourly blood-pressure chart and fluid-balance chart, and a half-hourly respiration chart. Over a period of three hours 1½ pints (850 ml.) of blood was given and the drip was continued as a slow intravenous 10% glucose infusion in order to improve the urinary output. Potassium citrate, 15 gr. (1 g.), and phenobarbitone, 1/2 gr. (32 mg.), were given every four hours.

At 6.30 p.m., three hours after admission, the blood pressure had risen to 98/60, the pulse was 90 and regular, and the patient felt better in herself, although she still had some pain over the lower pole of the uterus. By 10.15 p.m. she was feeling much better; her blood pressure had risen to 118/60, and her uterus was softer and less tender. The foetal presentation and position could be made out distinctly as vertex R.O.A. with the head unengaged. The foetal heart was not heard.

At 10 a.m. the next day (April 11) the blood pressure was 118/70 and the pulse rate 80, and the patient was quite comfortable. The urinary output for the previous 16 hours was 10 oz. (284 ml.) and the Esbach reaction had come down to 5 parts per 1,000. Four hours later the patient complained of a recurrence of the severe abdominal pain. She was again shocked, her pulse having risen to 124 and her blood pressure