Pus Cell Count in Other Conditions

A few additional cases of interest will now be mentioned. The first is that of a boy, aged 15 months, who had a septic sore on his foreskin, yet the number of pus cells per c.mm. was only 4. In a girl aged 10 years, suffering from haemorrhagic nephritis, there were 24 pus cells and 300 red blood corpuscles per c.mm. A boy, aged 7 years, with acute nephritis had 10 pus cells and 84 red blood corpuscles per c.mm. Another girl, aged 9½ years, who had just had scarlet fever, was found to have 282 (and on a second occasion 290) pus cells and 16 red blood corpuscles per c.mm. The last case in this series is that of a girl, aged 10 years, who had a vaginal discharge. The urine showed 192 pus cells per c.mm. on the first examination; twelve days later there were 500, but after efficient treatment for eight days the number was only 44—too low for Cuthbert Dukes's definition of "pyuria," but within his figures for "excess of leucocytes."

Numerical Definition of "Pyuria"

The question what figure should be considered to constitute "pyuria," and what figure separates normal from abnormal, is of considerable interest. From the above observations it is suggested that in boys figures of over 10 per c.mm., and in girls over 100 per c.mm., should be regarded as abnormal and of pathological significance—that is, "pyuria." The term "excess of leucocytes" would seem to be superfluous.

Necessity for Microscopical Examination

Another point is whether urine containing the low pathological figures can be recognized with the naked eye, and at what figure definite opalescence occurs. From the above investigations it was seen that figures over 200 per c.mm. represented just opalescent urine, while below that figure the urine was clear. It is a fallacy, therefore, to say that pyuria can be recognized by naked-eye examination of the urine; it requires a microscopical examination to settle this important point.

BACILLURIA IN NORMAL CHILDREN

A series of forty normal children was taken. Two specimens of urine were collected from each child, one in the ordinary manner, the other being obtained by collecting the urine in sterile test tubes after the penis or the vulva had been cleaned with boric acid lotion followed by sterile normal saline. The latter is referred to as the "clean" specimen. Cultures were put up on agar from both specimens, and incubated for twenty-four hours. The nature of the growth, if any, was then investigated, and the results classified in three groups.

Group 1 consisted of those children whose urine was sterile both in the clean and in the ordinary specimens. There were nineteen in this section—thirteen boys and six girls.

Group 2 consisted of fifteen children—five boys and ten girls. The clean specimens were sterile, but the ordinary specimens were contaminated. No organisms, therefore, were present in the urine of the children in this group. Organisms in the ordinary specimens must have been due to external contamination.

Group 3 consisted of four girls and two baby boys. In all *B. coli* were grown from both specimens.

In 90 per cent. of the twenty boys the clean specimens were sterile; if the infants are excluded—and it is very problematic whether it is possible to exclude contamination in these—100 per cent. had no organisms in their urine. The urine was sterile in 80 per cent. of the twenty girls.

Careful study of the three groups reveals that the proportion of girls to boys in each increases from Group 1 to Group 3, and that only in six girls were the ordinary

specimens not contaminated. This seems to be strong evidence that in the remaining 20 per cent. organisms were present in the clean specimens owing to some external contamination, and that it is much more difficult to obtain a clean specimen from a female child than from a male child. The fact that there were no boys (excluding infants) from Group 3 also favours this view. One may conclude that the presence of organisms in the urine of a child is abnormal, though it does not necessarily indicate a pathological lesion of the urinary tract.

SUMMARY

1. The presence of leucocytes in the urine of normal children does occur; in boys as many as 10 per c.mm. can be considered as being within normal limits; in girls as many as 100 per c.mm. (the urine having been collected without any precautions). Figures exceeding these should be regarded as having pathological significance.

2. The enumeration of pus cells by the method described above might be more widely adopted, as it forms an accurate means of following the progress of a case from day to day and of comparing one case with another.

3. Bacilluria does not occur in normal children.

My thanks are due to Professor Still for permission to publish particulars about some of these cases, and to Dr. W. P. H. Sheldon for his untiring help throughout these investigations.

REFERENCES

- ¹ Dukes, C.: *British Medical Journal*, 1928, i, 391.
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THERAPEUTIC EVALUATION IN THE
TREATMENT OF SYPHILIS

BY

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In estimating the amount of treatment which can be considered adequate for any case of syphilis, at least three elements must be taken into consideration: (1) the nature of the agents used; (2) the dosage given; and (3) the period over which they have been administered.

One syphilologist may find that in primary sero-negative syphilis cure can only be brought about by the administration, during a period of thirty-six weeks, of 12.6 grams of an arsenobenzene compound (Ab. C.) plus that of a bismuth preparation in which the metal content amounts to 7.2 grams. Another may claim that by adopting a different principle of treatment, and by using either the same or different agents, cure can be attained in twenty-six weeks by giving 10.35 grams of Ab. C. together with a bismuth preparation in which the total quantity of the element amounts to 1.28 grams. It is not necessary to consider here which of the two methods is correct, or if one is more accurate than the other. What it is desired to point out is that the mode of assessing the amount of therapy administered is unsound, and does not present a true picture of the position.

DOSAGE

The first point to observe is that the Ab. C. dosage is expressed in terms of the actual compound itself (not of the arsenic), whereas that of the bismuth takes cognizance only of the elemental content. Now the therapeutic potency of an arsenical agent in the treatment of syphilis does not vary directly with its arsenic content. Various compounds contain various amounts of the element, from 18 to 22 per cent. or more. The pentavalent arsenicals such as stovarsol and tryparsamide are of lower therapeutic value than the trivalents, although their respective arsenic contents are 27 and 25 per cent. The dosage of Ab. C. is regulated not by the amount of arsenic present,

but by the toxicity of the compound itself, and this again is not in proportion to the quantity of element. The toxic dose of arsenic is 0.12 gram, but the amount of Ab. C. which would require to be given to get that quantity of arsenic into a patient would be more than 7 grams. Yet poisoning can take place from the administration of an amount of Ab. C. very far short of that. Neither the therapeutic potency nor the toxicity of the organic arsenical agents can be expressed in terms of the contained arsenic.

The bismuth preparations show a similar picture with respect to their bismuth contents. The percentage of elemental bismuth may vary from 4 to 60 or more. And here again animal experiment and clinical observation show that therapeutic potency does not depend upon the amount of bismuth present. A preparation with a bismuth content of 50 per cent. may be of considerably lower value as a treponemicide than one with a content of only 20 per cent. Levaditi has recently shown that bivatol, which consists of basic α -carboxethyl- β -methyl nonoate of bismuth dissolved in a fatty vehicle, is easily the most potent bismuth preparation in our armamentarium, though it contains only 4 per cent. of the element. My clinical experience fully bears this out, and shows that bivatol is practically equal in power to an arsenobenzene compound. It seems quite clear that a statement of the amount of bismuth therapy given to a patient is meaningless when expressed in terms of the metal; 5 grams of bismuth administered in one compound may not have so high a therapeutic value as half that amount when given in another combination. Therapeutic value depends upon the "usability" of the contained metal.

STANDARDIZATION

The Medical Advisory Board of the British Social Hygiene Council has urged that some action should be taken to standardize and control bismuth preparations used in the treatment of syphilis. This is necessary, but it does not seem to be yet realized that any attempt at standardization based upon the bismuth content must be futile. I suggest that the only satisfactory way in which standardization can be brought about is by taking into account the chemotherapeutic indices of the various agents. The chemotherapeutic index is expressed as the maximal tolerated dose per kilo divided by the minimal curative dose per kilo. For example, if the former is 0.120 gram and the latter 0.004 gram, the equation would read:

$$\frac{0.120}{0.004} = 30 = \text{chemotherapeutic index.}$$

In other words, the minimal curative dose is one-thirtieth of the maximum tolerated dose.

There exists a very clear and direct ratio between the chemotherapeutic index (C.T.I.) of an Ab. C. or a bismuth preparation and its therapeutic value. The various groups of remedial agents may be arranged roughly according to their C.T.I.'s in the following descending order:

Agent	C.T.I.	Efficiency Scale	Therapeutic Value in Units
Ab. C. (Stabilarsan, N.A.B.)	16	100	1
Bivatol	12	75	0.75
Bismuth metal suspension	8	50	0.5
Tryparsamide, etc. ...	5	31	0.31
Mercury	1	6	0.06

The place of the agent upon the efficiency scale is proportional to the C.T.I., and so likewise is its therapeutic value. Ab. C. being the most potent, its therapeutic

value (T.V.) is taken as unity. The others are expressed as decimal parts of it.

Now in the therapy of syphilis regard must be had not only to the amount of drug given, but also to the time within which a certain dosage is administered. There is a two-dimensional "time-quantity" factor, which is of essential importance. It is best, in my view, to look upon the time element as consisting of one week. In that seven-day period one records that a certain number, or fractional parts, of therapeutic units (T.U.'s) have been given. It has to be assumed that whatever the amount administered it has been the optimum amount for that seven-day period. Thus if 0.45 gram of stabilarsan is given in one week a dose of 1 T.U. is recorded. Although 0.6 gram may be given the next week, that is also reckoned as 1 T.U. Similarly, in a child or delicate person, 0.15 gram is also 1 T.U. In the Salford Municipal Clinic the agents used are stabilarsan, bivatol, and tryparsamide or stovarsol. As will be seen from the above table, however much or little of stabilarsan, bivatol, or stovarsol is given during a period of seven days, it is reckoned as 1, 0.75, or 0.31 therapeutic unit respectively. The Salford routine course of treatment for a case of sero-negative primary syphilis is, according to the general method of reckoning, stated as follows:

Stabilarsan once weekly for 6 weeks (total 3.45 grams).
 Bivatol twice weekly for 4 weeks (total Bi 0.64 gram).
 Stabilarsan once weekly for 6 weeks (total 3.45 grams).
 Bivatol twice weekly for 4 weeks (total Bi 0.64 gram).
 Stabilarsan once weekly for 6 weeks (total 3.45 grams).
 Giving a total of 10.35 grams of stabilarsan and 1.28 grams of bismuth metal in 26 weeks.

The above, of course, conveys no idea whatever of the real therapeutic picture, because there is no relationship or comparability between grams of Ab. C. and grams of metallic bismuth so far as curative value is concerned. If, however, we state the treatment in terms of therapeutic units calculated as indicated above, we do get a useful comparison, thus:

Stabilarsan once weekly for 6 weeks (total 6 therapeutic units).
 Bivatol twice weekly for 4 weeks (total 3 therapeutic units).
 Stabilarsan once weekly for 6 weeks (total 6 therapeutic units).
 Bivatol twice weekly for 4 weeks (total 3 therapeutic units).
 Stabilarsan once weekly for 6 weeks (total 6 therapeutic units).
 Giving a total of 24 therapeutic units (stabilarsan 18, bivatol 6) in 26 weeks.

The number of therapeutic units given in a series of injections is the product of the number of weeks and the unit therapeutic value of the drug in question; thus, a four-week bivatol series is calculated as $4 \times 0.75 = 3$ T.U.

The Salford experience, then, is that the minimum amount of treatment necessary to secure a satisfactory percentage of cures in sero-negative primary syphilis is 24 therapeutic units given in twenty-six weeks.

APPLICATION TO OTHER COURSES

This system of evaluation may be applied to other courses of treatment. In several other treatment centres the minimum prescription for a sero-negative primary case is 12.6 grams of Ab. C. with 7.2 grams of bismuth metal in thirty-six weeks. The Ab. C. is given in two series of ten injections at weekly intervals, with a rest period between series. In this way 20 therapeutic units of Ab. C. are injected. Supposing that a bismuth metal suspension is used, the C.T.I. will be in the region of 8. This preparation would be allotted, therefore, the value of 50 on the efficiency scale, which means a therapeutic value of 0.5 T.U. Nine injections of this bismuth agent are given at weekly intervals concurrently with the Ab. C.—that is, eighteen weeks in

all of bismuth therapy. The total number of therapeutic units of bismuth given will then equal 18×0.5 —that is, 9 T.U. In this case we have the experience that a total of 29 T.U. must be given to obtain a satisfactory percentage of cures. On account of concurrent administration it is necessary to interrupt the treatment by rest intervals, so that thirty-six weeks are occupied in completing treatment, as against twenty-six at Salford.

The net therapeutic efficiency (N.T.E.) of treatment must take into account the time occupied in attaining cure, and this may be expressed by the equation:

$$\text{N.T.E.} = \frac{\text{Total therapeutic units} \times 100}{\text{Weeks occupied by treatment}}$$

Therefore

$$\text{Salford N.T.E.} = \frac{24 \times 100}{26} = 92$$

Whereas

$$\text{the other N.T.E.} = \frac{29 \times 100}{36} = 81$$

According to this scheme of reckoning there would appear to be a balance of 11 points of net therapeutic efficiency in favour of the Salford method, or, in other words, a saving of time of ten weeks, and of an appreciable quantity of remedial agent (5 T.U.).

It is not, however, my purpose here to open a controversy as to alternating *versus* concurrent treatment. I wish merely to suggest that a standardization of therapeutic values be made along the lines I have indicated; this might well be adopted by the Ministry of Health. Upon some standard animal experimentally infected, it is necessary to work out the chemotherapeutic indices of the various chemical agents. From these one could, in a way which is at present impossible, compare the relative values of different modes of treatment and go far towards settling the vexed question of what constitutes adequacy. Not until some such standardization is adopted will it be possible to check the tremendous amount of inefficient therapy that is now being prescribed in all good faith. I submit the foregoing suggestions as a "preliminary note" in the hope that they may stimulate someone with more competence and greater leisure than I have, to explore the paths indicated. I have here only attempted to enunciate general principles; the various details—mathematical, biochemical, and so on—can only be elucidated and proved by experiment.

Memoranda

MEDICAL, SURGICAL, OBSTETRICAL

FRACTURED NECK OF THE FEMUR TREATED BY INJECTION OF BLOOD

In an article on union and non-union of fractures¹ Blundell Bankart described a case of typical intracapsular fracture of the neck of the femur successfully treated by injection of blood into the site of the fracture, combined with reduction by skeletal traction. The object of the present note is to place on record another such case treated in the same way with a similar successful result.

A man, aged 34, fell from his bicycle in December, 1929, and was unable to use his left leg. After admission and x-ray examination elsewhere he was transferred to the Hospital of St. John and St. Elizabeth with all the signs of an intracapsular fracture of the neck of the left femur. There was considerable external rotation, but little shortening. Twenty-four hours after the accident blood was withdrawn from the median basilic vein and 10 c.cm. injected into the left hip-joint. The limb was then abducted and slung in a Hodgkin splint, and an extension of 15 lb. applied to the femur by

means of ice-tong callipers inserted under local anaesthesia. Subsequent x-ray examination showed a good position, and this extension was maintained for three weeks, when strapping extension of 8½ lb. was substituted. During the whole time the knee was kept movable by means of a knee flexion piece, and massage was given to the hip. A further radiogram six weeks after reduction showed a little new bone formation; all extension was then removed, and massage given to the whole leg for a further fortnight, during which time the patient was fitted with a walking calliper splint. After discharge he was able to return to his work at a lathe wearing the splint; it was finally omitted three months later, when a radiogram showed bony union in good position. All movements at the hip-joint were full and painless; flexion at the knee was possible to more than a right angle, and has increased since the calliper was left off.

Commentary

Even in young people these fractures show a tendency to non-union, and by ordinary methods of treatment must be immobilized for a long period. In this case there was both x-ray and clinical evidence of union after six weeks.

It is important that the blood should be injected into the joint itself; the average capacity of the adult hip-joint as estimated from a number of cases injected post mortem is 14 c.cm. When the point of the injecting needle is in the right place there is considerable resistance to the injection; in the case described by Bankart I was able to feel the fractured surface.

With a suitably adjusted extension and counterpoise of the leg the patient can remain sitting up in bed throughout the treatment.

The addition of a knee flexion piece from the outset is of considerable help in preventing stiffness of the knee later on.

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HODGKIN'S DISEASE WITH UNUSUAL ONSET

The following case appears worthy of mention on account of the rather unusual first symptom and of the rapid termination.

T. W. R., aged 47, a well-nourished and previously quite healthy man, noticed in February, 1930, that he was becoming hoarse. As the huskiness did not yield to simple remedies he had several carious teeth extracted. This procedure was followed by some slight enlargement of the glands in the neck. In June he was admitted to the Derby City Hospital as the hoarseness still persisted and the glands in the neck were increasing in size.

On examination, he was well developed and well nourished, but was rather anaemic in appearance. On both sides of the neck were present moderately large masses of discrete glands which had the general characteristics of lymphadenoma. His one complaint was that of hoarseness. Laryngeal examination revealed a nodule situated on the left cord and some general oedematous thickening of both cords, which were movable. No other glands were palpable apart from those in the neck, nor could the spleen be palpated. The Wassermann reaction was negative, and the blood picture showed a secondary anaemia with no marked increase in eosinophils.

A gland was removed from the neck under local anaesthesia, and the pathological report stated: "The gland is destroyed by a cellular tissue with relatively little stroma and large areas of necrosis. The appearances are suggestive of acute Hodgkin's disease." A screen examination of the chest showed a mass irregular in shape in the mediastinum. Some fourteen days after admission discrete glands appeared in both axillae. The glands rapidly increased in size, and ultimately caused extreme oedema of both arms. The patient's condition rapidly grew worse, and he died after just over one month in hospital and barely six months from the appearance of the first symptom. Whilst in hospital, the patient had a temperature of the Pel-Ebstein type.

¹ Bankart, A. S. B.: *British Medical Journal*, 1930, i, 8.