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THIRD INTERNATIONAL STANDARD FOR POSTERIOR PITUITARY

(RE-NAMED THIRD INTERNATIONAL STANDARD FOR OXYTOCIC, VASOPRESSOR AND ANTIDIURETIC SUBSTANCES IN 1956)

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SYNOPSIS

In October 1955, stocks of the Second International Standard for Posterior Pituitary were running low and the Department of Biological Standards of the National Institute for Medical Research, London, was asked to proceed with the arrangements for an international collaborative assay of material for the Third Standard. A single 142-g batch of posterior-pituitary-lobe powder was obtained and distributed in ampoules, in approximately 30-mg quantities. Samples were sent to 19 laboratories in 10 countries. In all, 185 assays were carried out, 122 for oxytocic activity, 53 for vasopressor activity and 10 for antidiuretic activity.

On the basis of the results, which were analysed statistically at the National Institute for Medical Research, it was agreed that the potency of the Third Standard (re-named International Standard for Oxytocic, Vasopressor and Antidiuretic Substances in 1956, in view of the recent synthesis of oxytocin and vasopressin) should be expressed as 2.0 International Units per milligram. The International Unit therefore remains unchanged as 0.5 mg of the dry powder.

The First International Standard for Posterior Pituitary was established by the Permanent Commission on Biological Standardization of the League of Nations Health Organization in 1935. The material for this Standard had been in use since 1926 as the British Standard for Extracts of the Pituitary Posterior Lobe, and consisted of an acetone-extracted dry powder prepared from fresh, dissected bovine posterior pituitaries. The unit of each of the oxytocic, vasopressor and antidiuretic substances was defined as 0.5 mg of the dry powder. The reasons leading to the decision to define units of the three activities in terms of one standard preparation are given in Memoranda M.36 and M.43 of the League of Nations Health Organization.[2]

By 1939, steps had been taken to replace the First Standard and about 50 g were prepared in an identical way and distributed in 30-mg amounts in 1500 ampoules. An international collaborative assay performed on this material revealed that the potency of each of the three activities was approximately 15% greater than those of the First Standard, but that the ratio of the three individually measured activities remained virtually the same. It was argued in the memorandum on the Second Standard that the slight increase in apparent potency represented " a closer approximation of the new Standard, at the date of comparison, to the ideal which was aimed at in the original definition of the unit, as the specific activity contained in 0.5 mg of the dry powder, obtained by the prescribed procedure from the perfectly fresh and cleanly dissected posterior lobe material ". By adhering to this process of preparation there was considered to be " no possibility, through a cumulative effect of such slight increases in the value of the unit at successive renewals, of increasing its value beyond that natural optimum ".

By 1955 the supply of the Second International Standard was running low, and in October of that year the WHO Expert Committee on Biological Standardization [23] asked the Department of Biological Standards at the National Institute for Medical Research, London, to obtain a preparation of posterior pituitary suitable as a replacement and to proceed with the arrangements for a collaborative assay. Suitable material for the new Standard was obtained through the generosity of the Armour Laboratories in the USA. The material consisted of a single batch of 142 g of bovine posterior-pituitary-lobe powder, prepared according to the method described for the two former Standards. It was received at the National Institute for Medical Research in a single amber-coloured glass container, in January 1956. The material was distributed into 2000 glass ampoules, each containing approximately 30 mg. The ampoules were then placed over P_2O_5 in a desiccator, constricted, filled with dry nitrogen in the usual way, and sealed. The moisture content (loss of weight at 60°C over P_2O_5 after 5 hours) on one of the ampoules was 0.15%. The ampoules have been stored in the dark at —10°C.

The excessively dry nature of this powder unfortunately makes it somewhat difficult to weigh out and handle.

Re-naming of the International Standard

Investigation during the past few years has brought to light the following new facts. Two pure peptides have been isolated from ox pituitaries and characterized as having the properties of oxytocin and vasopressin respectively.[10, 14, 18, 20] A difference has been found in the amino-acid constitution of pure oxytocin peptides from the ox and from the pig.[14, 20] These natural peptides, and a number of chemical homologues which also possess activity, have been synthesized.[9, 11-13] There is a difference in potency,

expressed in terms of units per milligram of pure peptides, between different animal species and between the different homologues which have been synthesized. In view of these developments, the WHO Expert Committee on Biological Standardization which met in October 1956 [24] changed the name of the Standard to the " International Standard for Oxytocic, Vasopressor and Antidiuretic Substances ". The word " substance " is used in spite of the recognized fact that the vasopressor activity and antidiuretic activity are due to the same peptide.

Collaborative Assay

In May 1956, 19 laboratories from 10 different countries were invited to take part in the international collaborative assay. A memorandum (see Annex 1) was distributed to these laboratories. The names of the participating laboratories are given in Annex 2, but elsewhere in this report they are distinguished only by a number which has no connexion with the order of listing in that annex.

Although there is now substantial evidence that vasopressor and antidiuretic activities are due to the same single substance, it was decided nevertheless to ask participants to carry out assays for all three activities as before.

Of the total 185 assay results which were received, two-thirds were oxytocic assays, and every laboratory but one contributed to this number. Four laboratories assayed the new Standard for each of its three major activities.

Table 1 summarizes the number of assays which were received from different laboratories.

Statistical Analysis

Each assay was analysed by a standard method appropriate to its design. The methods of analysis are often given in the papers which describe assay methods, references to which are given in Tables 2, 3 and 4.

None of the assays permitted a test for the linearity of the log-dose/response lines, but in many cases it was possible to test their parallelism. When the log-dose/response lines for the old and the new standard preparations departed significantly from parallelism, the assay was rejected as invalid.

An estimate of potency was made for each valid assay and this was weighted by the reciprocal of the variance of the log potency.

The estimates of potency which were obtained from each laboratory were tested for homogeneity within laboratories. When a heterogeneous set was encountered it was sometimes possible to reject a single aberrant value, the remaining potencies then being homogeneous. On some occasions there was no obviously discrepant value and then the total weight for that laboratory was reduced to the point where χ^2 became non-significant.

TABLE 1. NUMBER OF ASSAYS FROM DIFFERENT LABORATORIES

Laboratory No.	Number of assays			Total
	oxytocic	vasopressor	antidiuretic	
1	5	5	0	10
2	13	2	0	15
3	20	20	0	40
4	7	4	0	11
5	9	0	0	9
6	3	3	0	6
7	13	5	0	18
8	5	0	0	5
9	5	0	0	5
10	0	2	4	6
11	2	2	2	6
12	2	2	0	4
13	3	1	1	5
14	3	3	1	7
15	14	2	0	16
16	4	1	2	7
17	1	1	0	2
18	8	0	0	8
19	5	0	0	5
Total . . .	122	53	10	185

Each homogeneous set of potency estimates was combined to give a weighted mean potency for each laboratory, by use of the approximate formula

$$\bar{M} = \frac{\Sigma WM}{\Sigma W}$$

where M is the weighted mean log potency and M and W are the log potencies and weights, respectively, obtained from single assays.

The mean potencies (antilog M), total weights and the number of assays utilized in this estimation are given in Tables 2, 3 and 4.

Finally, the mean potency estimates from different laboratories were tested for homogeneity between laboratories and an over-all weighted mean potency calculated for each type of activity.

TABLE 2. RESULTS OF ASSAYS OF OXYTOCIC ACTIVITY

Laboratory No.	Number of assays	Potency (units/mg)	Weight	Method
1	5	1.78	10 455	Fowl blood pressure (Coon) [5]
2	6	1.90	39 398	Rat uterus (BP) [3]
2	6	1.97	84 398	Fowl blood pressure (BP) [3]
3	18	1.91	19 374	Rat uterus (BP) [3]
4	7	1.75	30 993	Fowl blood pressure (BP) [3]
5	9	1.90	5 581	Rat uterus (BP) [3]
6	2	1.89	12 395	Fowl blood pressure (BP) [3]
7	11	1.76	18 886	Fowl blood pressure (BP) [3]
8	5	1.88	8 152	Guinea-pig uterus (Dale) [6]
9	4	1.80	5 170	Rat uterus (Holton) [16]
11	2	1.92	4 483	Rat uterus (Holton) [16]
12	2	1.89	1 529	Fowl blood pressure (USP) [22]
13	3	1.75	11 154	Fowl blood pressure (USP) [22]
14	3	2.03	19 706	Fowl blood pressure (USP) [22]
15	13	1.75	63 337	Fowl blood pressure (USP) [22]
16	4	1.82	8 487	Fowl blood pressure (BP) [3]
17	1	2.84	1 790	Rat uterus (Holton) [16]
18	8	1.80	6 471	Guinea-pig uterus (Nielsen) [19]
19	5	2.07	11 847	Guinea-pig uterus (Dale) [6]
	114	1.87	363 606	

Results

Oxytocic activity

Laboratories 8, 12, 18 and 19 submitted assays of designs which were unsuitable for the calculation of individual weights. Separate estimates of potency were made for each assay, and a weight calculated directly from their variance. No tests of validity or homogeneity were possible.

Laboratories 13, 14 and 15 used designs in which they measured the response to two doses of the new Standard, but only one of the old Standard. Individual weighting and a test of homogeneity was therefore possible, but a test for parallelism was not.

The remaining laboratories all used two doses of each Standard, and, of the 82 assays of this design, six were rejected for non-parallelism (two

TABLE 3. RESULTS OF ASSAYS OF VASOPRESSOR ACTIVITY

Laboratory No.	Number of assays	Potency (units/mg)	Weight	Method
1	5	1.87	10 197	Rat (Dekanski) [7]
2	2	2.01	5 774	Rat (Dekanski) [7]
3	20	1.79	53 847	Cat (BP) [3]
4	4	1.79	20 771	Rat (Dekanski) [7]
6	3	1.78	4 666	Rat (Dekanski) [7]
7	5	1.89	3 179	Dog
10	2	2.00	8 974	Rat (Dekanski) [7]
11	2	2.01	2 340	Rat (Dekanski) [7]
12	2	1.53	5 206	Rat
13	1	1.97	6 479	Rat (USP) [22]
14	3	1.90	8 755	Rat (USP) [22]
15	2	1.71	7 595	Cat
16	(1)	Invalid	Invalid	Rat (USP) [22]
17	1	2.89	1 953	Rat (Dekanski) [7]
	52	1.84	139 736	

from each of Laboratories 3 and 7, and one from each of Laboratories 6 and 9).

The total weight for Laboratories 5 and 14 was reduced for heterogeneity, and for the same reason a single potency estimate was excluded from the final potency for Laboratory 15 and Laboratory 2 (rat-uterus method).

TABLE 4. RESULTS OF ASSAYS OF ANTIDIURETIC ACTIVITY

Laboratory No.	Number of assays	Potency (units/mg)	Weight	Method
10	4	2.02	4 763	Rat (Dicker) [8]
11	1	1.93	372	Rat (BP) [3]
11	1	2.16	268	Rat (Ginsburg & Heller) [15]
13	1	2.04	235	Rat (Stein) [21]
14	1	1.93	57	Rat (Burn) [4]
16	2	1.72	65	Rat (BP) [3]
	10	2.02	5 760	

The variability between potency estimates obtained by different laboratories was highly significant ($\chi^2 = 270$ with 18 degrees of freedom, $P < 0.001$). If, however, the over-all weighted mean potency is calculated a value of 1.869 units/mg is obtained. The potency of 2.84 units/mg for Laboratory 17 is the only one which is obviously different from the other potencies in Table 2. Since this value is associated with a comparatively low weight, its exclusion only reduces χ^2 to 211 and the mean potency for oxytocin to 1.865 units/mg.

It is obvious that the variation between laboratories is much greater than the error of the assay method and is also greater than the variation within laboratories. The reasons for this are not known.

The final potency estimate of 1.87 units/mg is therefore grossly overweighted and a calculation of limits of error, using the total weight of 360 000, would be meaningless.

Vasopressor activity

No tests of validity or homogeneity could be made for the assays from Laboratories 3 and 12 and weights were estimated directly from the variance of individual estimates of log potency. Laboratory 15 used only a single dose of each Standard and all the remaining assays were of a (2 + 2) design. Of these, none showed any significant departure from parallelism, but the assay from Laboratory 16 was rejected since the common regression was not significant.

The results from 9 laboratories were tested for homogeneity and of these only Laboratory 14 showed any sign of inconsistency. The total weight of 18 000 for this laboratory was therefore reduced to about one half.

The potency estimates from different laboratories were again heterogeneous ($\chi^2 = 160$ with 12 degrees of freedom) and the weighted mean potency was calculated as 1.836 units/mg (Table 3).

Exclusion of the low potency obtained by Laboratory 12 and the high one from Laboratory 17 reduced the value of χ^2 to 51, but left the mean potency almost unchanged at 1.837 units/mg.

Limits of error to the over-all potency of 1.84 units/mg have not been calculated for the same reasons as those given in the section on oxytocin assays.

Antidiuretic activity

All these assays were of standard (2 + 2) designs. There were no signs of invalidity or of heterogeneity within the two laboratories where repeat assays were carried out.

The estimates obtained by different laboratories could be validly combined to give a weighted mean potency of 2.015 units/mg (Table 4), since

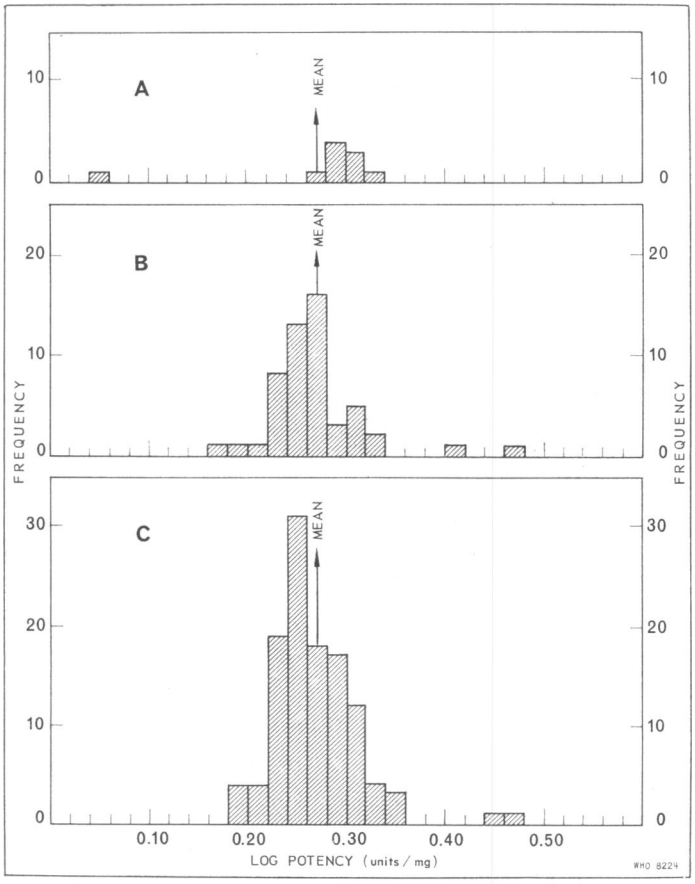
they were a homogeneous set ($\chi^2 = 0.72$ with 5 degrees of freedom, P = 0.98-0.99). The limits of error to the potency (P=0.95) are 1.896-2.141 units/mg.

Comparison of different activities

No formal test of significance can be made between the final potencies which have been estimated for the three activities, since it has not been possible to calculate limits of error to these potencies.

One way of overcoming this difficulty is to ignore the internal evidence of each assay and calculate the geometric mean potency and its limits directly from each distribution of individual log potencies (see figure below).

DISTRIBUTIONS OF INDIVIDUAL LOG POTENCIES



A = antidiuretic activity (10 assays)
B = vasopressor activity (52 assays)
C = oxytocic activity (114 assays)

Limits calculated in this way take into account all possible causes of variation between individual potency estimates.

It was found that this method of analysis led to final potencies for oxytocic and vasopressor activities which differed by only 1% from the weighted potencies, while the total variance was increased five-fold, as can be seen by a comparison of the total weights in Table 5.

TABLE 5. FINAL POTENCIES USING TWO DIFFERENT METHODS OF ANALYSIS

	Oxytocic		Vasopressor		Antidiuretic	
	weighted	unweighted	weighted	unweighted	weighted	unweighted
Potency (units/mg)	1.87	1.85	1.84	1.86	2.02	1.87
Weight	363 606	60 694	139 736	25 511	5 760	1 452
95% limits of error	—	1.82-1.89	—	1.80-1.91	1.90-2.14	1.66-2.12

There is comparatively little information available for antidiuretic activity, and it is therefore not surprising that different methods of analysis lead to potencies which differ by 8%. The weighted mean potency for antidiuretic activity is largely based on a single potency estimate of 2.04 units/mg, which was one of the four made by Laboratory 10. The weight of 3094 associated with this estimate was greater than the total weight for the other nine assays of this activity. As can be seen from the figure, the unweighted potency is considerably affected by one very low estimate. The unweighted mean potencies for the three activities are very consistent ($\chi^2 = 0.03$, P = 0.98-0.99).

Comparison with First International Standard

All the estimates which have been quoted so far have been based on the assumption that the Second International Standard possessed exactly two units of oxytocic, vasopressor and antidiuretic activity per mg.

As mentioned above, when the Second Standard was assayed it was found to be approximately 15% more potent than the First Standard, but it was thought desirable to leave the definition of unit activity unchanged.[2]

In the present study, the proposed Third Standard has been shown to be 7% less potent than the Second. It appears, therefore, that the new Standard is some 5% more potent that the original material which was used as the First International Standard.

The unweighted potencies have been used for the comparison of activities of the three standards (Table 6) since the results of the collaborative assay for the Second International Standard were analysed by a comparable method.

TABLE 6. COMPARISON BETWEEN THE ACTIVITIES OF THE FIRST, SECOND AND PROPOSED THIRD STANDARDS

	Oxytocic	Vasopressor	Antidiuretic
1st Standard	100	100	100
2nd Standard (in terms of 1st)	111.0	113.0	116.5
3rd Standard (in terms of 2nd)	92.7	92.8	93.7
3rd Standard (in terms of 1st)	102.9	104.9	109.2

Discussion

There seems no doubt that the proposed Third International Standard possesses oxytocic and vasopressor activities of the same magnitude, these being about 7% less than the corresponding activities of the Second Standard. The amount of information available for antidiuretic activity is insufficient to lead to any firm conclusion, but examination of the 10 results which were received gives no indication of any real difference between this activity and the other two. Moreover, it is known that antidiuretic activity is due to the same peptide as vasopressor activity, and so there is no reason to expect a difference between these two.

In reaching these conclusions a number of interesting side-issues have emerged. The first of these is the relative lack of precision of antidiuretic assays. Using the weight per assay as a measure of precision it will be seen that oxytocic and vasopressor assays are equally precise, giving average weights of about 3000, while the average weight for an antidiuretic assay is less than 600. Even this low value is considerably boosted by the contribution from one laboratory. It is therefore likely that some 250-500 antidiuretic assays would be required in order to assess this activity to the same precision that has been attained for vasopressin.

Most laboratories have been able to repeat their estimates of potency within the limits of error of the assay. There is, however, significant variation between the potency estimates obtained by different laboratories. Such variation is often encountered in collaborative assays and may be partly due to variations in weighings and dilutions. Laboratory 17 has estimated both oxytocic and vasopressor activities at a level which is so much higher than that found by the other laboratories that there is a suspicion of some mishap of this kind. The other estimates all fit well into symmetrical bell-shaped distributions (see figure, page 332).

In order to provide estimates of potency with associated limits of error for each activity, it is necessary to take the heterogeneity between laboratories into account. One possibility is to reduce the weight for each laboratory until χ^2 becomes non-significant, but leaving the weighted mean

potency unchanged. Alternatively, the semi-weighting method of Bliss [1] could be used. This would produce a result between the fully-weighted and unweighted means in Table 5. It has been noticed previously by Humphrey et al.[17] that, when a large number of assay results are available, a direct estimate of the over-all potency from the distribution of individual log potencies gives the same result as the lengthy analysis and subsequent weighting of individual assays.

It is satisfactory to see that any of the methods of analysis described above lead to final potency estimates for oxytocin and vasopressin which vary only very slightly about 1.86 units/mg.

Re-definition of the International Unit

It appears that there are two alternative courses that it is possible to take in ascribing a potency to the new Standard.

(*a*) To follow the established custom of assuming that the earlier Standard was exactly of the potency it was labelled (2.0 units/mg) and defining the activity of the new Standard in terms of the best estimate obtained from the collaborative assay (1.86 units/mg).

The unit would then be defined as the activity contained in 0.54 mg.

(*b*) To retain the same potency for the Third Standard as for the Second. This would have obvious advantages in simplicity of use and would be repeating the step taken in 1942, as mentioned above and explained in the memorandum on the establishment of the Second Standard.[2] It has been shown that the relative potencies for the three activities agree remarkably well, maintaining the original ratio of 1 : 1 : 1. This indicates that the material is essentially similar to both the First and the Second Standard.

The Third Standard is undoubtedly less potent than the Second. Its relationship with the First Standard is not so clear, since, at the intermediate step of the establishment of the Second Standard, it appears that the results were not reported in detail as they have been in the present assay and the most that could be claimed in the memorandum was that the margin of superiority (of the Second Standard over the First) was probably between 10% and 20%. Even assuming that the mean potencies and standard errors given in the memorandum were entirely correct, the values for the Third Standard in terms of the First as shown in Table 6 have rather wide limits of error, as there has been a double conversion in their calculation; for example, the 5% limits to the estimated potency of 102.9% for oxytocin are 97.2% and 108.9%, a range which includes the assumed value of 100% for the First Standard. The only conclusion that can be reached is that there is probably no significant difference between the activities of the First and the Third Standard, with a bias towards a slight superiority for the latter.

To define the unit as the activity contained in 0.50 mg would therefore be in keeping with the material used until 1942. On the other hand, it might perhaps be more justified to use this figure if the Third Standard had proved to be more potent, not less, than the Second Standard, in view of the stated aims of the creators of the First Standard that 2.0 units/mg should represent the maximum potency obtainable in any material prepared from ox pituitaries in the same way as the original.

Finally, it should be reiterated that the synthesis of oxytocin and vasopressin has opened the way to the provision of pure chemical standards. Consequently, the life of a Standard, composed of a relatively crude extract, may now be short. In these circumstances, the aims of the creators of the First Standard are not, perhaps, so vital, and a decision to maintain the unit at 0.5 mg may well prove the more attractive course for the limited future.

Conclusion

In view of the above arguments, it has been agreed among participants in this assay that *the potency of the Third International Standard for Oxytocic, Vasopressor and Antidiuretic Substances shall be expressed as 2.0 units per milligram, that is, one unit equals 0.5 milligram.*

Annex 1

INSTRUCTIONS TO PARTICIPANTS IN COLLABORATIVE ASSAY

The WHO Expert Committee on Biological Standardization which met in October 1955 asked the Department of Biological Standards at the National Institute for Medical Research, London, to obtain a preparation of posterior pituitary suitable as a replacement for the existing International Standard, stocks of which are running low, and to proceed with the arrangements for a collaborative assay. Suitable material for the new Standard has been obtained through the generosity of the Armour Laboratories in the USA. It is proposed to compare this new preparation with the existing Standard by an international collaborative assay in the usual way.

The proposed International Standard consists of a single batch of 142 grams of posterior-pituitary-lobe powder, which was received at the National Institute for Medical Research in a single amber-coloured glass container on 11 January 1956. The material was stored at 4°C for 5 weeks and was then distributed in approximately 30-mg amounts into 2000 glass ampoules. The ampoules were left *in vacuo* over P_2O_5 for 10 days; they were then constricted, stored for 14 days, filled with pure, dry nitrogen and sealed. The moisture content (loss of weight at 60°C over P_2O_5 after 5 hours) on one of the finished ampoules was 0.15%.

Since distribution, the ampoules have been stored at —10°C.

The collaborative assay

It is suggested that each participant should carry out assays on this material for:

(*a*) oxytocic activity;

(*b*) antidiuretic activity;

(*c*) vasopressor activity.

Any recognized method of assay is suitable, but at least one of the methods should be a biological one and should satisfy the following criteria:

1. In all cases the assays should be designed so as to provide from their own internal evidence an estimate of the potency of the unknowns in terms of the Standard, and fiducial limits to that estimate. This entails testing at a minimum of 2 dose-levels of both Standard and unknown.

2. The design should ensure that factors known to cause variation are eliminated, when such factors cannot otherwise be adequately controlled.

No statistical analysis need be undertaken by participants. The results should be sent in their original form to the Department of Biological Standards at the National Institute for Medical Research, London, where the over-all analysis will be carried out.

Details of preparations

Three ampoules, containing approximately 30 mg each of the proposed International Standard, together with three ampoules containing approximately 30 mg of the current International Standard, are available to each participant.

The materials should be used as they are supplied, without further drying and without undue exposure to moisture.

Details of dispensing

A portion of the dried powder, corresponding to about 20 units, is transferred rapidly from the sealed ampoules to a weighing-bottle, and the bottle is at once closed. The powder is weighed. It is washed into a dry, hard-glass boiling-tube with one-half as many millilitres of a mixture of 0.25 ml of glacial acetic acid and sufficient water to produce 100 ml as there are units present in the quantity of powder taken. The top of the boiling-tube is plugged with cotton wool, and the tube is placed for five minutes in briskly boiling water. The tube is quickly cooled, and the liquid is filtered through a dry filter-paper into another hard-glass tube. The filtrate is an extract of the standard preparation, and contains 2 units per ml. The filtrate may be distributed into a series of sealed glass ampoules, and sterilized by being placed in boiling water for three minutes. It is stored at 0°C, and remains unchanged in activity for six months. It must not be used as a standard later than six months after preparation. It is diluted ten times with normal saline solution immediately before use.

Participants taking part in the assay for oxytocic, antidiuretic and vasopressor activity, or on any one or more of these, should send their results to the Department of Biological Standards, National Institute for Medical Research, London, N.W.7. The results will be analysed statistically and a report submitted to the WHO Expert Committee on Biological Standardization, after comment by participants in the collaborative assay.

Annex 2

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RÉSUMÉ

Le troisième étalon d'hormone de lobe postérieur d'hypophyse a été préparé sous le nom d'étalon international de substances ocytociques, vasopressives et antidiurétiques. Ce changement de nom est motivé par le fait que deux peptides pures, l'une ayant les propriétés de la vasopressine, l'autre celles de l'ocytocine ont été maintenant synthétisées.

Un total de 142 g de poudre de lobe postérieur d'hypophyse a été réparti entre 19 laboratoires de 10 pays, qui ont effectué 185 essais. D'après l'analyse statistique des résultats, l'unité internationale a été définie comme correspondant à 0,5 mg de poudre sèche.

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