Radioimmunoassay of Hormones, Proteins and Enzymes

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THE VALIDITY OF SERUM TSH MEASUREMENTS BY IMMUNOASSAY

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According to Roget's Thesaurus, validity can be found among the synonyma for section 494 - Truth. Validity implies accuracy and preciseness and likewise authenticity. Authenticity of TSH, as determined by RIA may be affected by

- incomplete elimination of cross-reaction of the antibody with e.g. LH, FSH, HCG and their subunits,
- non specific interference of antigen-antibody interaction e.g. endogenous antibodies against TSH,
- immunoactive material lacking bioactivity and
- unexplained factors.

Some of the reasons for the lack of authenticity will be dealt with by other contributors during this meeting. The rest of this paper will be devoted to the elucidation of accuracy and precision of the radioimmunoassay for TSH.

It is not possible to apply the methods of quality control (Q.C.) in clinical chemistry (12), as there are no definitive or standard methods, except for a few steroids. The Q.C. of proteohormones is important, in view of the multiplicity of antisera and standard material at present in use. It has been demonstrated that the introduction of reference preparations alone has not led to a standardisation of results from hormone immunoassays. The assay method itself plays a much larger role, e.g. the length and type of incubation, the bound/free separation method, the antiserum, the way in which the tracer is prepared and the medium in which the standards are dissolved (3). Because of these problems, a model of external quality control survey (EQCS) was developed in this laboratory which allowed differentiation between systematic and random errors. During the past six years this concept has been enlarged and is now known as the "Munich-Model for External Quality Control of Hormone Assays" (4,7,8,1o).

The"Munich-Model" for EQCS has four strong points:

(1) Testing the accuracy against international reference preparations (proteohormones) or pure substances(T_3, T_4, cortisol).
(2) Pinpointing probable systematic errors in an assay system (effect of incubation, standard-solute, data-processing).
(3) A critical but constructive analysis of each participant's data - together with the setting up of a "two-way" contact if needed.
(4) An "automatic policing" of the kit-market without the need for legislative intervention!

The survey here described was carried out in 1977/78.

EQCS - PLANNING AND EXECUTION

(a) Preparation

Members of the German Societies f.Endocrinology and Clinical Chemistry, together with kit-producers, state hospital laboratories and private laboratories were invited to participate in the survey. The participant list was fully representative of all laboratory types in the Federal Republic of Germany. Three quarters of all letters had been answered within 4-5 weeks of dispatch.-Serum from clinically relevant patient groups was collected in advance, together with TSH-free serum (all sera with a tracer-binding of 1oo-11o % in the house assay). All sera were filtered through an asbestos filter under 5 Bar N_2 to remove fibrin clots and bacteria. The collection period was between 3 and 4 months. The participants were notified in a second letter of the date of dispatch for the samples.

Twenty samples of 1 ml were sent in dry-ice by express post. Table 1 shows the composition of the EQCS-sera. The main point here is, that the hidden standard curve was of MRC 68/38 TSH in human-TSH-free serum. Two sera contained TSH-antibodies, which probably arose from patients who had received injections of bovine TSH at some period in the past. Two samples from another EQCS, run by the German Society for Clinical Chemistry were kindly donated by Dr.G.Röhle and Professor H.Breuer,Bonn, FRG. A detailed questionaire was sent together with the serum samples, which covered the laboratory method of the TSH assay and space for the raw data (counts and concentrations for the laboratory internal standard curve and for the 2o EQCS sera).

(b) Data Processing, Notification of Performance

Return of results took place around 4 months after the data had been received. Because of all the raw data returned (see above), it was possible to standardise the data processing of the standard curve (curve I) - using a spline function (6,9). This allowed a comparison with the laboratory-own data processing, as well as the comparison between laboratory own standards and the hidden standard curve (curve II) using MRC 68/38 TSH in human TSH-free serum.

The data from each participant was transferred to punch cards (27-32 per participant) and read into a computer (Siemens 4o4/3). The computer program scheme and data-flow diagram have already been published in detail (1o). The results from each participant were printed on 6 sides of computer paper and returned to the participant with a set of histograms for all 2o samples showing anonymously the distribution of the values measured by all participants. This was accompanied by an explanatory

TABLE 1. Composition of the 2o samples for the EQCS.

Sample No.	Content
1	Hidden standard curve - 1o μU/ml TSH (MRC 68/38) in human TSH-free serum
2	Bonn-EQCS No.4 - sample B II
3	Pool serum - intra-assay control
4	Pool serum - intra-assay control
5	Pool serum in lower range containing native antibodies
6	Pool serum in upper range
7	Byk-Mallinckrodt-Thyroid Normal Control Serum
8	Pool serum in mid-range containing native antibodies
9	Hidden standard curve - 5 μU/ml TSH
1o	Hidden standard curve - 2o μU/ml TSH
11	Hidden standard curve - O μU/ml TSH
12	Hidden standard curve - 2,5 μU/ml TSH
13	Hidden standard curve - 1,25 μU/ml TSH
14	Bonn-EQCS No.4 - sample A II
15	Pool serum - intra-assay control
16	Hidden standard curve - o,62 μU/ml TSH
17	Pool serum - intra-assay control
18	Byk-Mallinckrodt - Thyroid Hyper Control Serum
19	Hidden standard curve - 4o μU/ml TSH
2o	Pool serum at upper limit of standard curve

All standards were dissolved in human TSH-free serum.
Samples 3,4,15 and 17 were identical.

letter and by a detailed evaluation of his performance. Full details are given elsewhere (1o). - The support of this study by the BMFT is acknowledged.

RESULTS

PERFORMANCE OF PARTICIPANTS AND METHODS

From 82 returned sets of data, 8 were only partly usable, the other 74 being subjected to computer analysis. In spite of the fact that the number of university clinic laboratories was the highest (n=24), this group did not constitute the majority of laboratories as in the first EQCS in 1976 (8).

The intra-assay coefficients of variation (c.v.) for the samples 3,4,15 and 17 were better than in 1976 (8), only 21 laboratories (28 %) having an intra-assay c.v. above 15 % for 4 samples of the identical serum. The range of c.v. was 1.22 - 59.5 % (mean 4.64 µU/ml).

Eleven different kits together with a variety of "own methods" were used by the participants. Table 2 shows the kits and the main assay details.

TABLE 2. List of kits with incubation times and separation techniques (Stand 1978).

Manufacturer	Separation technique	Incubation (h)
Diagnostic Products Corporation	2.Ab + 4 %* PEG	2,25 or 5,5
Corning	1.Ab bound to glassbeads	+2,o
Byk-Mallinckrodt	2.Ab	36
CIS (Isotopen Dienst West)	2.Ab bound to cellulose	+16-2o
Beckman	2.Ab	6,o
Henning	2.Ab	24 or 72
Abbott	18 % PEG	21
Kabi	2.Ab	+96
Behring	2.Ab solid-phase	36-48
Schwarz-Mann (Becton-Dickinson)	2.Ab	5,25
Phadebas (Pharmacia)	2.Ab coupled to dextrose	36-48
Bio-Rad	2.Ab solid-phase	5,o

+ These methods have no preincubation

* PEG = Polyethyleneglycol (Mr 6ooo)

Figure 1 was chosen to demonstrate some important points found in this survey. It shows the distribution of values measured for a serum (no.12) containing 2.5 µU/ml MRC 68/38 in human TSH-free serum:

- The accuracy of many methods is not acceptable as seen by the mean value of 4.o2 ± 1.86 µU/ml.
- The absolute values of TSH measured differ widely, although most kits calibrated their standards against MRC 68/38. Obviously, using the same standard is not enough to guarantee correct results.
- The standard deviation of the measured mean represents an inter-laboratory c.v. of 46.3 %. This c.v. is better than in 1976 (8), however is not yet satisfactory.
- The figure shows indirectly, that many kits are not able to measure 2 µU/ml TSH, however, this is of importance for thyroid function tests e.g. in order to measure the subnormal increase of TSH after TRH stimulation.

Beyond this, none of the methods (Tab.2) had an average c.v. under 25.5 % for the range O - 4 µU/ml

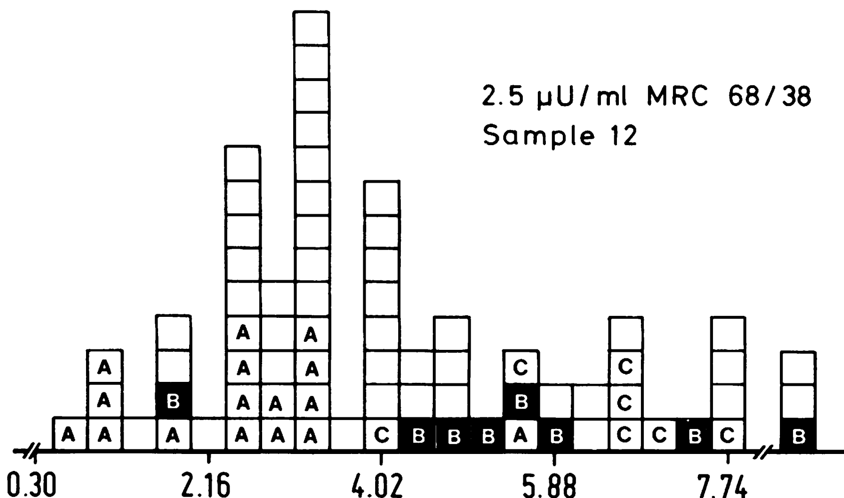

Figure 1. All measured values for sample No.12. The mean value and the two standard deviation range are shown. Further explanation see text.

(range of c.v. = 25.5 - 55.7 %),which must be rated as unsatisfactory. No kit has the robustness for the lower range as desired by EKINS (1).

METHODOLOGICAL STRATEGY

The tracer binding of the participant's own-method zero standard was compared with that of serum no.11 set at 1oo %, to check the binding effect due to the standard matrix alone. Three participants had values above 11o %, whose assays could be rated as too insensitive. 39 participants (53 %) showed acceptable zero-binding between 9o and 11o % and almost half, namely 32 participants, had values under 9o % giving rise to a "high blank" effect, i.e. elevated values in the lower range of the standard curve. These data corroberate that in accordance with earlier observations (3,8) only human TSH-free serum is optimal as matrix for the standard curve.

Figure 1 containing all measured values for sample no.12 allows a further conclusion, that only kit A showed a symmetrical Gaussian distribution of concentrations around the expected value. This kit used a preincubation, had standards in TSH-free human serum and a classical double-antibody method of separation of bound and free antigen. Kits with a short incubation time - under 6 h - the so called "same day assay" kits are shown as B and kits with no preincubation are shown as C. Both B and C kits are less sensitive and less accurate than the A kit,

confirming earlier objections (2) to very short assays (insufficient incubation time) and over-simplification (e.g. no cold pre-incubation).

The method used for bound/free separation plays a decisive role in cases where antibodies are present in serum. The kit using 18 % polyethylene glycol (PEG) showed binding well over the zero standard in sera 5 and 8, i.e. "negative" TSH values. The double antibody methods can also give false results inasmuch as the native antibodies compete with the test-anti-TSH. The second antibody, however, only precipitates the antiserum raised to human TSH, leaving the native antibody-TSH-complexes in solution, thus giving rise to false results (Tab.3). The easiest way to detect a native antibody to TSH in serum samples would be to measure the unspecific binding using PEG-precipitation after incubation of the serum with tracer.

TABLE 3. Effect of native antibodies on TSH values (µU/ml; mean ± SD).

Sample No.	Expected value	all participants	PEG	2.Ab(1)	2.Ab(2)
5	ca. 5 µU/ml	8.81 ± 4.o9	0	5.o3±1.71	15.7±5.56
8	ca. 1o µU/ml	1o.6 ± 7.o1	0	9.65±1.91	1o.2±1.29

(1), (2) Two kits as examples.

STEPS TOWARDS ACCURACY

Table 4 shows the regression-data from 74 participants from whom a computer-evaluation was possible. The values for the correlation-coefficient (r) and the regression line y = a + bx are given.The comparison of own results vs. curve I shows only the difference in the data-processing (own method vs. spline function). Here around 3/4 of all methods are comparable ($r > o.99$; $-1.o < a <$ $+1.o$; $1.1 > b > o.9$). The comparison of curve I and curve II shows the influence of the sum of all assay method details. Deviations from r = 1.oo reveal random errors in the system. In this survey 78.4 % of all participants had an r-value of above o.99, showing a good correlation. Deviations from a = 0, the intercept point on the x-axis, show a parallel displacement of the standard curve when r and b approach 1.oo. In this survey 68.9 % of all participants had an acceptable a-value. Deviations of b from 1.oo reflect the steepness of the standard-curve (accuracy). The larger the deviations of b from 1.oo, the worse the superimposibility of own and hidden standard curves. Here only 27 % of all participants had acceptable b-values (o.9o - 1.1o).This reflects the non-optimal state of affairs in the TSH-assay at the time of this EQCS!

One of the main achievements of this type of survey

TABLE 4. Regression data:
Own results vs curve I and
curve I vs curve II
Regression equation: y = a + bx

Parameter and boundaries	Own results vs curve I		Curve I vs curve II	
	n	(%)	n	(%)
r > o.99	59	(79.7)	58	(78.4)
o.95 - o.99	8	(1o.8)	14	(18.9)
< o.9o	7	(9.5)	2	(2.7)
Range	o.62 -	1.o	o.49 -	1.o
a > 1.o µU/ml	7	(9.5)	8	(1o.8)
-1.o to +1.o µU/ml	53	(71.6)	51	(68.9)
<-1.o µU/ml	14	(18.9)	15	(2o.3)
Range	-3.41 -	7.15	-1o.5 -	3.95
b > 1.1o	17	(23.o)	13	(17.6)
o.9o - 1.1o	53	(71.6)	2o	(27.o)
< o.9o	4	(5.4)	41	(55.4)
Range	o.75 -	1.36	o.47 -	1.43

Ideal values: r = 1, a = 0, b = 1.

is the possibility to select "reference laboratories" on the basis of their performance. Ten laboratories participating in this study (own method, n=4; kit A, n=6) had an ideal superimposibility of their own standard-curve with the hidden standard-curve. The data returned by the "reference laboratories" for samples no. 7,18,14,2 (Tab.5) may be considered as "assigned values". These assigned values obviously have a higher degree of accuracy than the median, target or mean values currently in use.

DISCUSSION

Two organisations are authorised to carry out EQCS in the FRG for clinical chemistry parameters and to give out certificates for the parameters which have been measured with acceptable accuracy (11). Both organisations, namely the German Society for Clinical Chemistry (DGKCh) and the Institute for Standardisation and Documentation in the Medical Laboratory (INSTAND) also carry out EQCS for hormones. For these, two lyophilised serum samples are sent to each participant for analysis of several components. These results are worked out (using different statistical

TABLE 5. Assigned values for 4 samples from 1o "Reference Laboratories" compared with values from other EQCS. TSH levels in µU/ml.

Sample No.	Median value (DGKCh-EQCS)	Target value (Byk-Mall.)	Mean value all partici- pants- this survey	Assigned value "Reference Labo- ratories"
7	-	+7.5±2.5	++8.22±2.75	++6.93±1.16
18	-	16.1±4.o	14.9 ±5.22	11.6 ±1.72
14	2.1	-	2.65±1.53	2.13±o.88
2	16.6	-	17.2 ±3.9o	15.2 ±1.94

+ - values represent mean ± 2 SD

++- values represent mean ± 1 SD

approaches) and returned to the participant. Advantages of such surveys are their ease to carry out and the frequency at which they can be repeated. Disadvantages are the lack of reference methods, leading in turn to a lack of "target-values". When, to take an extreme case, the majority of laboratories find values for the analyte concentration which are too high, those who estimate the analyte correctly have values lying either outside the -2 SD value or under the 2o-%ile.

The situation on the steroid sector ist almost ideal, in asmuch as a definitive method (isotope dilution mass spectrometry - IDMS) can be used to establish true values. A more intensive variation of this type of EQCS is run by the World Health Organisation Human Reproduction Unit (WHOHRU), (5). Here, 2 samples from a large set of serum pools (15-2o sera) are distributed at regular intervals over a period of 2 or 3 years, which allows for a continuous precision control of the participant's assays. The collection and storage of the large amounts of serum needed is the drawback of this survey.

The disadvantages of the "Munich-Model" of EQCS are evident for both participant and organizer, resulting in the infrequent repeat for each hormone every 2-3 years. For a small group, the amount of work is far too much to carry out regular EQCS of this model,which can only be performed for one, at the most two, parameters. The advantage is the detailed analysis of methodology leading to detection of errors and establishing a two way contact between organizer and participant. Furthermore, this type of EQCS survey can be used to select reference laboratories on the basis of objective criteria and to establish assigned values.

A compromise would be to use both types of EQCS, where the Munich-Model set the target values in 1o-2o serum pools,which could then be used in a WHOHRU-type long

term EQCS. Furthermore, the reference laboratories chosen from the Munich Model EQCS could work with matched reagents in order to set the target values even more accurately, these matched reagents being either an organisor-produced or commercially-produced kit.

The time taken in setting target values for 6 hormones in the serum pools must be estimated at 18-24 months. In the eyes of the authors, such an undertaking in the FRG is only possible in conjunction with the DGKCh and INSTAND, and eventually together with kit producers.

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